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NEPHROLOGY

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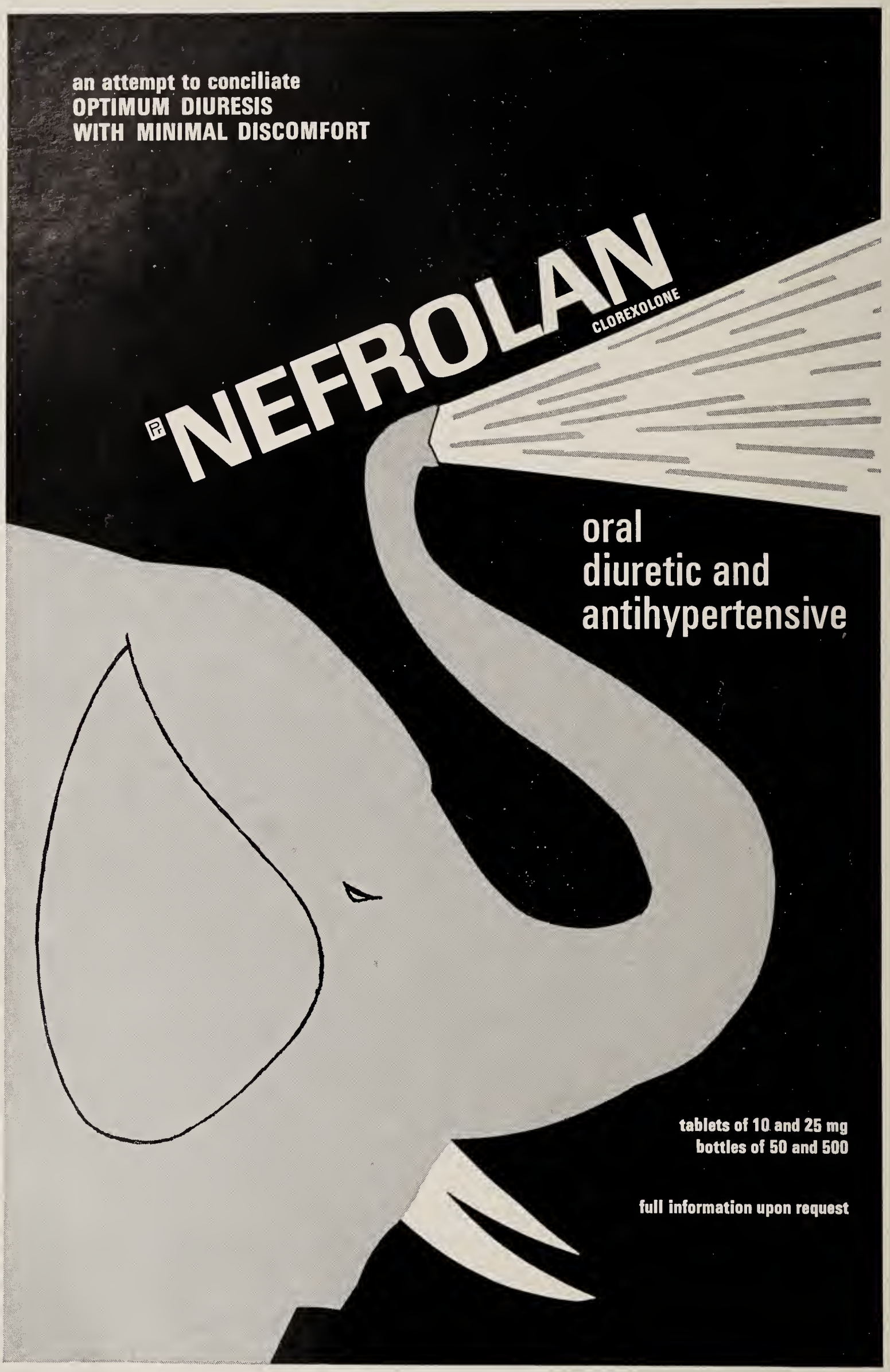
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Mechanism of action analogous to that of chlorothiazide
Prolonged diuretic action

According to numerous clinical trials carried out in Europe and in Canada, its main indications are the following:

EDEMA OF VARIED ETIOLOGY — CARDIAC FAILURE — HYPERTENSION (used alone or with other antihypertensive drugs)

dosage and administration

Orale route — single dose or divided doses. Adjust dosage, frequency and duration of administration according to patient's needs. Dosage guide for adults:

Various edemas and cardiac failure:

25 to 50 mg daily on alternate days or on 3 consecutive days per week; in rare cases, daily dosage may reach 100 mg. Maintenance doses: 10, 20 or 25 mg daily may be adequate.

Water retention of a mild degree (as in pre-menstrual syndrome): 10 mg daily or 25 mg three times a week.

Hepatic cirrhosis: 25 to 75 mg, occasionally increased to 100 mg daily, for 3 to 4 days. **A potassium supplement should always be given.**

Hypertension: in mild or moderately severe cases, Nefrolan often exerts a hypotensive action when used alone: 10 mg daily should be tried initially and the dose increased to 20 mg if the response is inadequate. In some cases, a dose of 10 to 20 mg on alternate days or three times a week may be sufficient. Higher dosage may be used if necessary or other antihypertensive drugs added to the treatment.

supportive treatment

a) **Potassium supplement** — Nefrolan may cause potassium depletion. The daily ingestion of fruits rich in potassium is suggested. **A daily potassium supplement of 1 to 3 g is recommended: in hepatic cirrhosis — when a digitalis preparation is being administered — during prolonged corticosteroid therapy.** In patients treated with Nefrolan for periods exceeding 2 to 3 weeks, frequent monitoring of serum potassium, chloride and bicarbonate levels should be performed. Supplements of potassium should be given when indicated.

b) **Spironolactone** may be associated with Nefrolan when the urinary output of sodium chloride is low and there is reason to suspect aldosteronism.

side effects

The only relatively frequent side effects are nausea (more rarely vomiting) **and anorexia** (particularly in ambulant patients).

Symptoms associated with hypotension and low serum potassium may be encountered when antihypertensive and/or diuretic drugs are used, and are not specific for Nefrolan. So far, the drug has had no demonstrable adverse action on the liver, kidneys, blood-forming organs or blood-sugar levels. At diuretic doses, a few cases of urticaria have been reported. Nefrolan may give rise to a lowered serum potassium and, in rare instances, to a hypochloremic and hypokaliemic alcalosis proceeding to tetany. The drug may increase blood uric acid and precipitate an attack of gout in predisposed patients. The loss of body fluid may cause thirst, frequency of micturition, constipation and dryness of the lips.

contra-indications and precautions

Those of the thiazide diuretics in general:
adrenal insufficiency; renal impairment; severe hepatic disease; in heart disease, it must be borne in mind that a lowered blood potassium increases the sensitivity of the myocardium to digitalis. If the urinary output is insufficient treatment should be discontinued as accumulation in the body may occur. Nefrolan should be used with caution in patients predisposed to gout. There is no clinical evidence that fetal abnormality has resulted from treatment with Nefrolan during the first trimester of pregnancy; however in the present state of our knowledge, it is recommended that the drug be withheld in early pregnancy. Nefrolan has been very little used in pediatrics; data available is insufficient to recommend its use in children.

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1. Simpson, F. O.: Clinical trial of a new oral diuretic, M & B 8430. Current Therap. Res., *6*, (1), 21-26, January 1964. — 2. Baba, W. I. *et al.*: Studies on the mechanism and characteristics of action of a new phthalimidine diuretic, clorexolone. Clin. Pharmacol. Therap., *7*, (2), 212-223, March-April 1966.—3. Nenna, A. and Mariambourg, A.: Appréciation des résultats obtenus dans la pratique médicale courante par l'utilisation du diurétique 12 833 R. P. Gaz. Méd. France, *73*, (9th suppl.), 48-51, May 10 1966.—4. Mary, P. and Mirouze, J.: Essai clinique de la clorexolone salidiurétique 12 833 R. P. (flonatril). Semaine Thérap., *42*, (9), 529-532, November 1966.

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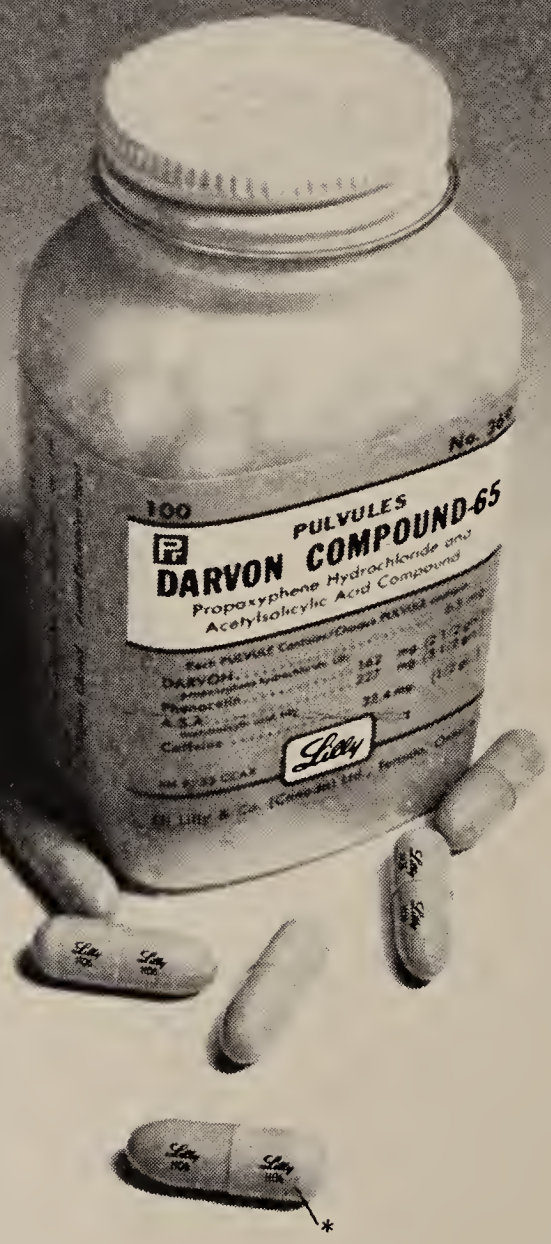

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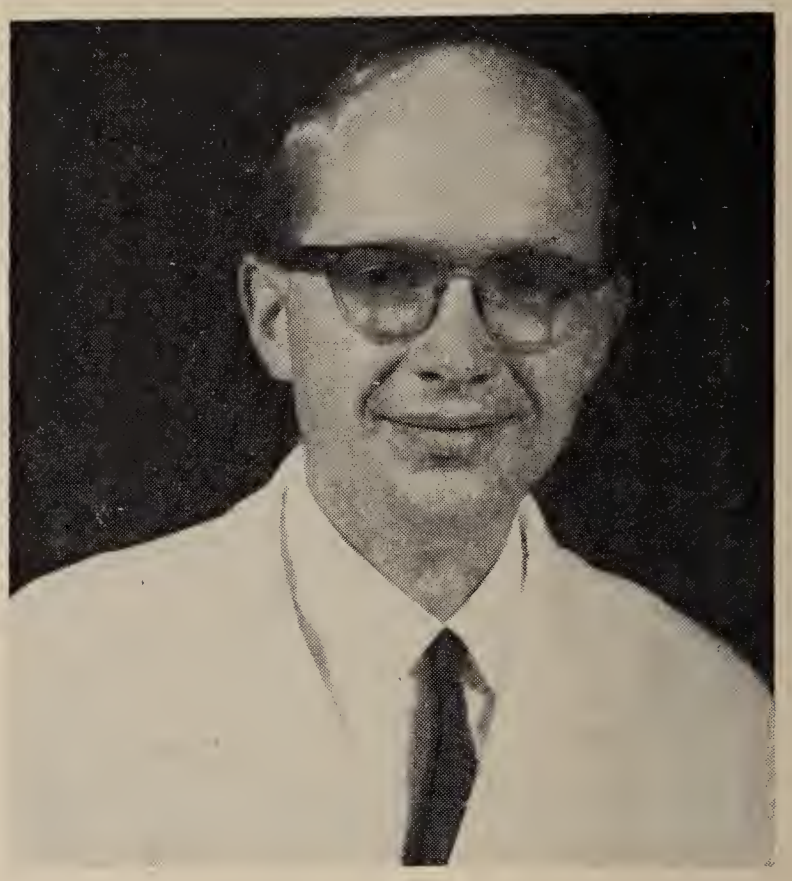
Guest Editorial



Dr. Douglas R. Wilson graduated in 1959 from the Faculty of Medicine, University of Toronto. He obtained his F.R.C.P. in 1964, and moved to Boston for two years where he performed micropuncture studies on diseased kidneys. In 1967, he worked in London studying the effects of renal failure on electrolyte metabolism.

Dr. Wilson is presently an Associate in Medicine at the University of Toronto, and is continuing his investigations of the pathophysiology of renal disease. He hopes to establish a renal transplant program at the Toronto General Hospital in the near future.

What Is Nephrology?

The study of the normal and diseased kidney has interested physiologists, biochemists, physicians and surgeons for many years. The human kidneys, weighing less than a pound, receive one-quarter of the total cardiac output and form 38 gallons of plasma ultra-filtrate per day. All but one quart of this filtrate is reabsorbed by the renal tubules, along with two pounds of salt, one pound of baking soda, one-half pound of sugar, and many other substances which are essential to the body economy. It is little wonder that the processes by which these impressive feats are accomplished have intrigued renal physiologists and bedevilled medical students!

Despite centuries of speculation it was not until the historic micropuncture studies of Richards and his colleagues in the 1920's that proof was obtained of the manner in which urine was formed by glomerular ultrafiltration, tubular reabsorption, and tubular secretion. Clearance techniques which were popularized by Homer Smith provided a means of measuring the efficiency of the whole kidney in performing these functions in relation to various substances. In 1951 Wirz, Hargitay and Kuhn first presented experimental evidence for the countercurrent multiplier theory of urine concentration which has added greatly to our understanding of renal pathophysiology. In recent years the widespread application of micropuncture techniques to the study of individual nephrons has clarified the normal function of various parts of the renal tubule and these methods are now being used to study the etiology of the abnormalities found in certain renal diseases such as the oliguria of acute renal failure and the concentrating defect in hypokalemic nephropathy.

For those with a basic interest in biochemistry the energy metabolism of renal tissue and its relation to the transport of electrolytes across cell membranes is providing a fruitful field of investigation. Oxygen consumption by the kidney has been shown to be directly related to sodium reabsorption by the renal tubules, this function being the principle metabolic work of the kidney. In this single organ there are sharp contrasts in metabolism, that of the cortex being aerobic, oxidative, and utilizing fatty acid as

the principal substrate, while that of the medulla is largely anaerobic, glycolytic and utilizes glucose. Changes in the acid-base status of the whole animal have been shown to affect gluconeogenesis and enzyme activity in renal tissue. It remains a considerable challenge to discover the alterations in cell metabolism which form the basis for the abnormalities found in renal disease.

Nephrology has become fully developed as a branch of clinical medicine since the revolutionary development of chronic intermittent hemodialysis and renal homotransplantation in the past ten years. The use of permanent indwelling arterio-venous fistulas permitted repeated hemodialyses to be done easily and has provided an extension of useful life for a large number of relatively young people dying from renal failure. Moreover, the study of this group of patients has already added greatly to our knowledge of the hypertension, anemia, peripheral neuropathy, and disturbances of calcium and carbohydrate metabolism associated with uremia. The development of relatively safe immunosuppressive drugs provided a major breakthrough in renal homotransplantation which has enabled a reasonable percentage of patients to survive this procedure and remain well for a year or more. The discovery of methods for quickly determining the tissue compatibility between donor and recipient, for effectively preserving cadaver kidneys for longer periods, and for more selectively depressing the immune processes, hold the keys to the future in this exciting area.

In the attention given to chronic hemodialysis and renal transplantation, however, we must not forget the importance of further study of the early stages of renal disease which precede by many years the onset of renal failure. In acute glomerulonephritis the immunologic pathogenesis and mechanism of progression to the chronic stage require much further study as investigations of the role of complement, of the immunoglobulins, and of fibrinogen deposition in the glomerulus provide clues. The development of the pathologic picture of chronic pyelonephritis in the absence of demonstrable urinary tract obstruction or infection is an equally great enigma but bacterial protoplast formation, temporary abnormalities in motility of the urinary system, or the effects of nephrotoxins, such as phenacetin, may be found to be important. Many other fascinating problems bckon to the clinical nephrologist: the familial nephritides, the systemic diseases and electrolyte disturbances affecting the kidney, the renal tubular disorders, the metabolic aspects of renal calculi and the endocrine functions of the kidney in producing substances which elevate blood pressure (renin-angiotensin), lower blood pressure ("medullin") and stimulate erythropoiesis (erythropoietin).

Let me conclude by suggesting that the study of the kidney offers "something for everyone", whether you are interested in membrane transport across the tubule wall or in designing a better artificial kidney for use in the home!

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Editorial

Although this Journal has met with success primarily as a vehicle for student expression, the editors felt that its effectiveness for the reader could be enhanced if, part at least, were devoted to clarifying important topics for which insufficient time was alloted at the undergraduate teaching level. The editors hope that Volume XLV will help solve this problem, in addition to still providing material of more academic interest for the advanced readers. In the new feature "Fundamentals of Radiologic Examination", we believe a step has been made to attain this goal. Hopefully, this innovation will make the Journal more readable, interesting, and instructive to all levels: from the neophyte medical student to the graduate. Due to ever increasing pressures to consolidate basic knowledge, many students now find extensive perusal of academic journals to be both time-consuming and of dubious immediate value.

The editors invite comments from the readers regarding first, the relative value of an undergraduate journal as an educational medium and second, the degree to which this purpose is served by *this* publication in particular.

D.A.L. W.K.L.

The Functioning Nephron In Health

M. A. Robinette 6T8

Many years ago, Aristotle stated that the kidneys were not vital organs, but rather their function was to provide a "greater finish and perfection to the body". It was soon realized that the kidneys, not the bladder, were the site of urine production; however the explanation of the mechanisms of the formation of urine awaited the development of micropuncture techniques and methods of analysing minute samples of tubular filtrate. Thus, modern renal physiology is only about thirty years old, and continues to be a field of intensive research.

It is the purpose of this article to review in a practical manner the basic processes involved in the elaboration of urine: ultrafiltration, reabsorption, and secretion.

ULTRAFILTRATION

In Bowman's capsule, there exists a net force driving fluid through the fenestrations in the endothelial lining of the capillaries. This fluid passes through the basement membrane and then around the podocytes of the epithelial cells into the beginning of the proximal tubule.

The basement membrane is now believed to be the ultrafilter, laid down and maintained by the podocytes. The glomerular fluid entering the proximal tubule is an ultrafiltrate because it is virtually protein-free, yet contains all the crystalloids in the same concentration as plasma.

The Dynamics of Ultrafiltration

The filtration pressure is the net result of the osmotic and hydrostatic forces acting at the capillary membranes. Those tending to encourage filtration into Bowman's capsule are:

(i) the hydrostatic pressure in the capillaries (70 mm. Hg).

(ii) the osmotic pressure of the ultrafiltrate (negligible).

Those tending to hinder filtration into Bowman's capsule are:

(i) the hydrostatic pressure within the capsule (15 mm. Hg).

(ii) osmotic pressure of colloid in the capillaries (25 mm. Hg).

Thus, under normal conditions, there is a net force of 30 mm. Hg [70 - (25 + 15) mm. Hg] forming glomerular ultrafiltrate.

Glomerular Filtration Rate

The glomerular filtration rate (G.F.R.) is the total amount of glomerular ultrafiltrate produced each minute. It is normally 125 ml./min.

Since the filtration rate is directly proportional to the filtration pressure, alterations in the osmotic and hydrostatic forces mentioned above are reflected in the rate of glomerular filtration:

(i) changes in the hydrostatic pressure in the capillaries:

- a. changes in systemic blood pressure
- b. afferent or efferent arteriolar constriction.

(ii) changes in the hydrostatic pressure within Bowman's capsule:

- a. ureteral obstruction.

(iii) changes in the osmotic pressure in the capillaries:

- a. hypoproteinemia
- b. dehydration.

The glomerular filtration rate also depends upon both the permeability of the basement membrane and the area of the glomerular capillary bed. For example, in the nephrotic syndrome, there is an increase in the basement membrane permeability with a corresponding increase in G.F.R., and in chronic nephritis, there is a decreased capillary bed, and therefore a decreased G.F.R.

Clearance

The clearance of a substance is a measure of the efficiency of the kidney in excreting it, and is represented by the number of millilitres of plasma that can be cleared of that substance during a one-minute passage through the kidneys. Clearance is expressed by the following formula:

$$\frac{Ux \cdot V}{Px} = \frac{\text{quantity of "x" excreted in 1 min.}}{\text{concentration of "x" in 1.0 ml. plasma}}$$

$$= \text{clearance of "x"}$$

Ux = concentration of "x" in 1.0 ml. urine (mgm./ml.)

V = volume of urine formed per minute (ml.)

Px = concentration of "x" in 1.0 ml. plasma (mgm./ml.)

(i) *Inulin Clearance*

Inulin is a polysaccharide which is freely filterable, neither reabsorbed nor secreted by the tubule cells, biologically inert, and accurately measurable in both urine and plasma.

If the concentration of inulin in the urine is 125 mgm./ml., and the rate of urine formation is 1 ml./min., then their product is the amount of inulin excreted each minute. Dividing their value by the concentration of inulin in plasma, one obtains the volume of plasma cleared of inulin each minute. The clearance of a substance like inulin, which is neither reabsorbed nor secreted, must equal the G.F.R.; the amount of inulin appearing in the urine each minute must have been provided by filtering an equal amount of plasma.

Although the inulin clearance test appears to be the most accurate measure of G.F.R. in man, it involves the infusion of an exogenous substance which is chemically difficult to measure and is therefore arduous and time-consuming.

(ii) *Creatinine Clearance*

Creatinine, a waste product of creatine and phosphocreatine, appears endogenously in the blood and urine in relatively constant amounts, and thus is a more simply conducted test for G.F.R. than is the inulin clearance.

A falsely high plasma creatinine determination results from interference by non-creatinine chromogens (creatinine is measured colourimetrically), therefore tending to *decrease* the clearance value by increasing the denominator "Px". This, however, is offset by the secretion of creatinine by the kidney tubules, therefore tending to *increase* the clearance value by increasing the numerator "Ux"; thus the endogenous 24-hour creatinine clearance test is a good approximation of G.F.R. in most instances.

REABSORPTION

At a glomerular filtration rate of 125 ml./min., 180 litres of ultrafiltrate are delivered to the proximal tubule each day. Since this volume represents about four times the total body water, it is evident that much of this filtrate must be reabsorbed in order to conserve both water and electrolytes. The processes involved are intimately linked to the maintenance of a normal blood volume, electrolyte concentration, and pH.

Types of Reabsorptive Mechanisms

(i) *Passive Transport*

This refers to the migration of substances in the direction of the electro-chemical gradients, with no energy being expended. Examples of this type are the reabsorption of water secondary to the osmotic force created by sodium reabsorption, and reabsorption of chloride secondary to the electrical force created by sodium reabsorption.

(ii) *Active Transport*

This refers to the movements of substances against an electrochemical gradient, with work being performed by the cells effecting the transport. There are two types of active reabsorptive mechanisms:

a. those with transport maxima (Tm):

These systems are capable of reabsorbing substances only up to a fixed amount per minute. Once this maximum transport is exceeded, the system is saturated, and the substance begins to appear in the urine. Examples of this type are the reabsorption of glucose (which has a Tm of 375 mgm./min.), phosphate, sulphate, amino acids and uric acid.

There are certain hereditary diseases characterized by transport system deficiencies, such as the Fanconi Syndrome with amino-aciduria, glycosuria and phosphaturia.

b. those with gradient-time limitation:

The transport of sodium is not limited to a fixed number of mEq. which can be transported each minute, but rather is limited by the size of the *gradient* which can be established by the sodium pump across the tubular wall during the *time* that the luminal fluid is in contact with the epithelium.

Although chloride and bicarbonate are passively reabsorbed, they both exhibit the gradient-time limitation indirectly, because their reabsorption is dependent upon that of sodium.

Reabsorption by the Proximal Tubule

During its passage down the proximal tubule, the ultrafiltrate is normally reduced in volume to about 20% of its original value, due to the reabsorptive mechanisms describe above.

Sodium is actively reabsorbed, with chloride following passively due to the electrical potential created by the sodium pump. Water is reabsorbed passively by the osmotic force established by sodium and chloride reabsorption, and therefore the osmotic pressure of the tubular fluid remains isotonic with respect to plasma.

Reabsorption by the Loop of Henle

The ability to elaborate a urine hypertonic to plasma is endowed only to mammals and birds, and since these phyla are the only ones possessing loops of Henle, it was thought for a long time that this was where urine was concentrated. As well, it was noted that the length of the loops varied in direct proportion with the ability to concentrate urine. However, with the development of micropuncture techniques, the tubular filtrate in the

distal tubule was always found to be either slightly hypotonic or isotonic—never hypertonic. The collecting ducts must therefore be the site of urine concentration, with the loops of Henle facilitating the process.

The loop of Henle, with a descending limb that is freely permeable to both sodium and water, and an ascending limb which actively transports sodium yet is impermeable to water, acts as a countercurrent multiplier system. This creates a hyperosmotic medullary interstitium which allows the formation of a hypertonic urine in the collecting ducts providing their epithelium becomes permeable to water under the influence of antidiuretic hormone (A.D.H.)

(i) *Nature of the Countercurrent Multiplier*

Filtrate entering the descending limb from the proximal tubule is isotonic (about 300 mOs./L.) and filtrate leaving the ascending limb is slightly hypotonic (about 200 mOs./L.). At the tip of the loop of Henle, however, the osmotic pressure is 1200 mOs./L. The increasing hyperosmolarity as the loop descends in the medulla is dependent upon the ascending limb being impermeable to water yet capable of pumping sodium into the interstitium. This raises the solute concentration of the interstitial fluid, and decreases the concentration in the ascending limb. Sodium diffuses passively into, and water out of the descending limb, according to the osmotic gradients. Because of the position of the two limbs, a small osmotic gradient created by the sodium pump in the ascending limb is multiplied as the loop descends into the medulla. (see Fig. 1.) Thus, the descending limb and surrounding interstitial fluid become increasingly hypertonic until at the tip of the loop deep in the medulla, both the filtrate and interstitial fluid have an osmotic pressure which has been multiplied four times its original value. As the loop ascends, the osmotic pressure becomes increasingly less, until in the early distal tubule the filtrate is slightly hypotonic.

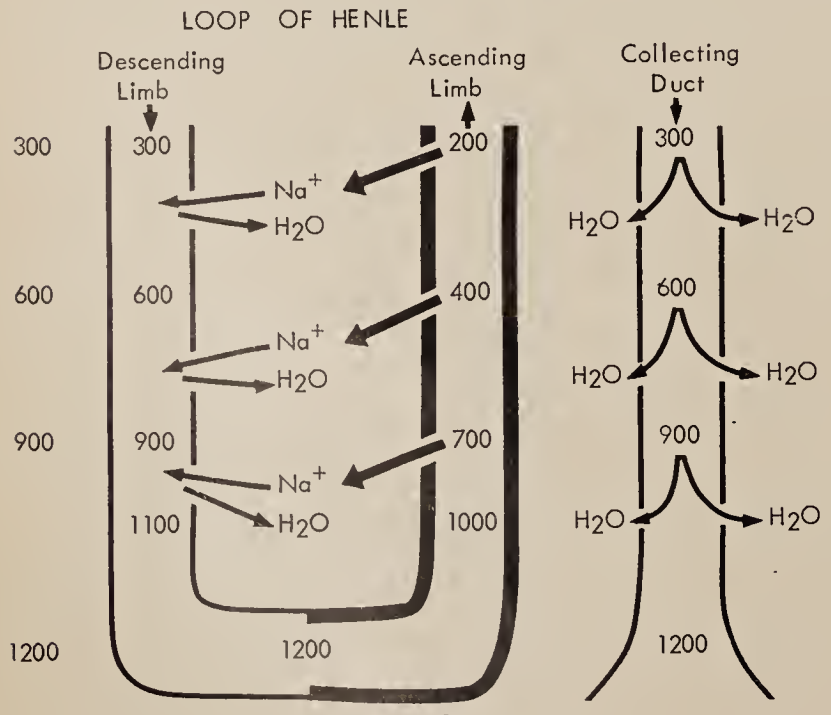

FIG. 1.

(ii) *Nature of the Countercurrent Exchanger*

The *vasa recta* are the capillary loops accompanying the loops of Henle. They form a similar hairpin turn deep in the medulla, and act as countercurrent exchanges. Blood entering the capillary loop with an osmotic pressure of 300 mOs./L. is subjected to the increasing osmolarity as it descends into the medulla. Thus water diffuses out, and osmotically active substances diffuse in. In the ascending limb, the process is reversed. What in effect occurs is that water by-passes the capillary circuit by diffusing directly across the top of the loop.

It is because of this mechanism of countercurrent exchange and because blood flow through the *vasa recta* is sluggish, that the solutes are "trapped in" and the osmotic gradients in the medulla are not removed by the circulation.

Reabsorption by the Distal Tubule and Collecting Duct

The sodium pump transport system which operates in the proximal tubule, also functions similarly in the distal tubule and collecting duct, with the exception that transport systems for the renal regulation of acid-base balance are added. The latter will be discussed later.

Through most of the distal tubule, the filtrate undergoes isotonic reabsorption thereby remaining slightly hypotonic to plasma. In the last part of the distal tubule and in the collecting duct, the filtrate is altered towards further hypotonicity or towards hypertonicity depending upon the titre of antidiuretic hormone (A.D.H.).

(i) *Water Diuresis*

In the presence of a low titre of A.D.H., the end of the distal tubule and the collecting ducts become impermeable to water. Sodium continues to be removed from the filtrate by the distal tubule and collecting ducts, and water remains behind. The result is a hypotonic urine, which can be maximally diluted to about 30 mOs./L. (equivalent to a 10-fold dilution of plasma).

(ii) *Water Conservation*

In the presence of a high titre of A.D.H., the end of the distal tubule and the collecting ducts become permeable to water. As the ducts pass through the medulla toward the papilla, the high osmotic pressure in the interstitium created by the countercurrent multiplier results in the diffusion of water out of the collecting ducts. The result is a hypertonic urine which can be maximally concentrated to about 1200 mOs./L. (four times that of plasma).

Under normal conditions, there is a titre of A.D.H. such that the filtrate that remains after passing through

the collecting duct amounts to 1.2 litres/day (0.5% of the total filtrate). This is now urine and is excreted into the pelvis of the kidney; and from there down the ureters to the bladder for storage.

SECRETION

A wide variety of organic acids and bases are eliminated from the body by glomerular filtration and tubular secretion, the latter serving as an accessory means of removal. Of more importance is the tubular secretion of hydrogen ions which forms an integral role in the renal regulation of acid-base balance.

Mechanism of Tubular Secretion

The mechanisms for tubular secretion are essentially similar to those for tubular reabsorption, the main difference being the direction of transport.

(i) *Passive Secretion*

This implies secretion of a substance down an electrochemical gradient, and occurs by a process called "diffusion trapping". The renal tubule cells are permeable to the undissociated weak acid or base, but are relatively impermeable to their ionized forms.

Undissociated weak bases will diffuse passively into the filtrate providing it is acidic, thereby providing the weak bases with hydrogen ions to form cations to which the tubules are impermeable (i.e. the cations are *trapped*). Thus, the excretion of weak bases (quinine, quinacrine, chloroquine, ammonia, etc.) is greatly facilitated by an acidic tubular filtrate.

Conversely, undissociated weak acids such as salicylic acid and phenobarbital diffuse into an alkaline filtrate where they release hydrogen ions and become anions to which the tubules are impermeable.

(ii) *Active Secretion*

This occurs against an electrochemical gradient, and is of two main types similar to the active reabsorptive mechanisms.

a. those with transport maxima (Tm):

Only two secretory mechanisms of this type are known. One secretes a group of compounds most of which are carboxylic or sulphuric acids (hippurate, creatinine, phenol red, p-amino hippurate (P.A.H.), penicillin, chlorothiazide, probenecid, various acetylated sulphonamides, several glucuronides and a group of urological contrast agents). All these substances compete for the same secretory system; this was utilized during the war when penicillin was scarce and probenecid was given to decrease penicillin secretion, thereby raising its blood level.

The other system secretes certain strong organic bases including thiamine, choline, histamine, quinidine, piperidine and hexamethonium.

b. those with gradient-time limitation:

Sodium is reabsorbed in the distal tubule in exchange for either potassium or hydrogen ions; because sodium reabsorption is by a gradient-time limited mechanism, therefore potassium and hydrogen are secreted by a similar means.

The potassium that is filtered through the glomerulus is almost completely reabsorbed by the proximal tubule, with that appearing in the urine resulting mainly from secretion by the distal tubule cells. Potassium and hydrogen ions compete with each other for exchange with sodium. Therefore with acidosis, the hyperkalemia that develops is due in part to the decreased potassium secretion as a result of the increased hydrogen ion secretion.

Renal Regulation of Acid-Base Balance

In the proximal tubule cell, bicarbonate is reabsorbed in large amounts secondary to the sodium-hydrogen exchange mechanism; in the distal tubule and collecting ducts, this continues secondary to the sodium-hydrogen or potassium exchange mechanisms. It is important to realize that these transport systems are not a means of ridding the body of endogenously-produced hydrogen ions; rather hydrogen ions are produced for the purpose of conserving sodium and bicarbonate.

Of the 50 to 70 mEq. of hydrogen ion formed each day by metabolism, one-third is excreted in the form of titratable acid (primarily sodium monophosphate), and two-thirds are excreted by the ammonia reaction. Thus, it is by these mechanisms that the filtrate becomes acidified in the distal tubule.

(i) *Reabsorption of Bicarbonate* (see Fig. 2.)

In both proximal and distal tubular cells, bicarbonate and hydrogen ions are formed from carbonic acid by the carbonic anhydrase (C.A.) catalysed reaction. The hydrogen ion (or the potassium ion in the distal tubular cell only) is exchanged for sodium which is then reabsorbed and enters the peritubular fluid along with the bicarbonate formed from the C.A. reaction. The hydrogen ion combines with bicarbonate already in the luminal fluid, and forms carbonic acid which dissociates into carbon dioxide and water, the former being reabsorbed. Thus, bicarbonate is conserved and hydrogen ion is excreted as water.

(ii) *Formation of Titratable Acid* (see Fig. 3.)

The carbonic acid formed in the distal tubular cell by the C.A. reaction, dissociates into a hydrogen and bicarbonate ion. The hydrogen ion is exchanged for sodium which is reabsorbed and enters the circulation along with the bicarbonate formed by the C.A. reaction. The hydrogen ion combines with the monosodium phosphate radical in the luminal fluid, and is excreted mainly as monosodium hydrophosphate.

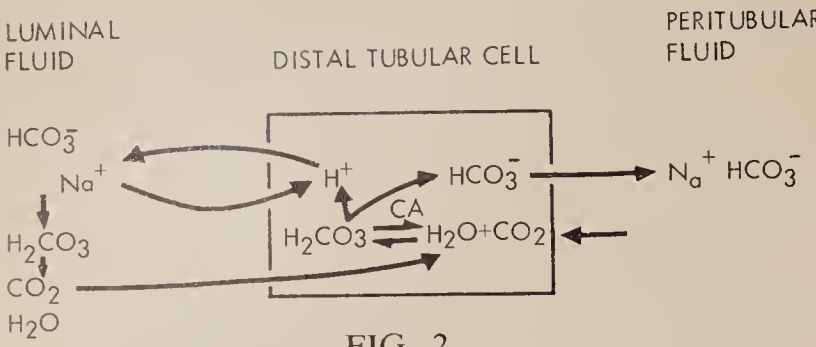

FIG. 2.

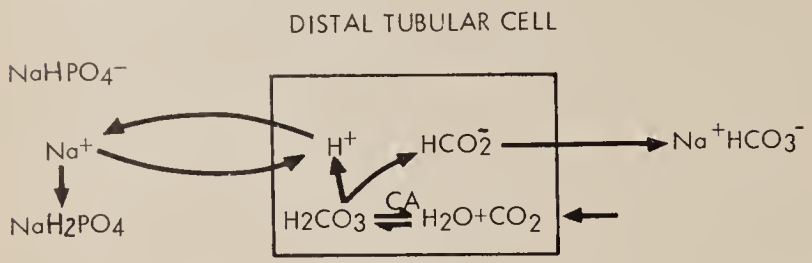

FIG. 3.

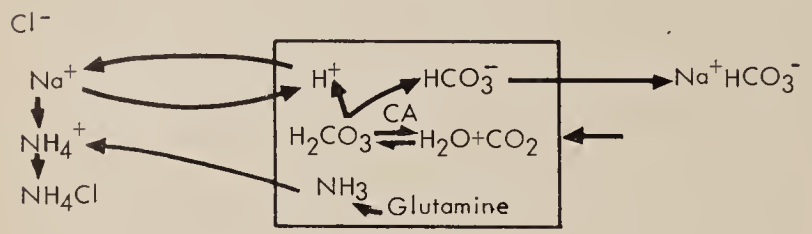

FIG. 4.

(iii) *Secretion of Ammonia* (see Fig. 4.)

In response to an acidosis, the distal tubular cell forms extra amounts of ammonia primarily from glutamine by the enzyme glutaminase. The ammonia is secreted into the luminal fluid where it combines with a hydrogen ion that has been exchanged for a sodium ion, and is excreted as ammonium chloride. This is a slow adaptive process which in the presence of an "acid load" may last about a week before the excess acid is completely excreted.

SUMMARY

A protein-free ultrafiltrate, containing all the crystalloids in the same concentration as plasma, is produced as a result of the hydrostatic pressure in the capillaries driving fluid through the glomerular membranes. The glomerular filtration rate is directly proportional to the glomerular filtration pressure, and factors affecting one, necessarily affect the other. The rate of glomerular filtration, normally 125 ml./min., is an important parameter of renal function; for as G.F.R. falls, so uremia with its associated retention of urea, creatinine, uric acid, sulphate, phosphate, potassium, etc. becomes more severe. G.F.R. is accurately measured by inulin clearance and approximated for practical purposes by creatinine clearance.

The ultrafiltrate is isosmotically reabsorbed by the proximal tubule by active and passive transport systems. In the loop of Henle, there is little net change in the osmotic pressure of the filtrate. However, an increasing osmotic gradient is established as the loop descends into the medulla by means of the countercurrent multiplier effect. This is endowed to the loop of Henle because its ascending limb actively transports sodium out but is impermeable to water, and its descending limb is permeable to sodium and water. The filtrate delivered to the distal tubule is hypotonic and remains this way or becomes isotonic until it reaches the collecting duct, depending upon the titre of A.D.H. The high osmotic gradients, established by the countercurrent multiplier and maintained by the countercurrent exchanger, create a force capable of drawing enough water out of the collecting ducts as they pass through the medulla to form hypertonic urine. Water is variably reabsorbed from the ducts depending upon the titre of A.D.H.

Although many substances are secreted by the nephron, of particular importance is the secretion of hydrogen and potassium ions, and how these are related to the renal regulation of acid-base balance. Three main renal tubular systems act to control blood pH: reabsorption of bicarbonate, excretion of titratable acid, and secretion of ammonia.

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The Pathophysiology Of Chronic Renal Failure

S. Nitzkin 6T8

The pathophysiology of chronic renal failure can best be studied by examining the alterations which occur in the normal excretory and regulatory functions of the kidney.

The complex functions of the kidney include:

1. Excretion of nitrogenous waste products of protein catabolism.
2. Excretion of acid.
3. Regulation of salt and water balance.
4. Regulation of potassium balance.
5. Regulation of blood pressure.
6. Stimulation of red blood cell production.
7. Calcium and phosphorus metabolism.
8. Excretion of many drugs.

Consequence of chronic renal failure may include:

1. Retention of protein wastes—azotemia.
2. Metabolic acidosis.
3. Disturbances in salt and H_2O balance (overhydration, edema, dehydration, sodium depletion).
4. Hyperkalemia and hypokalemia.
5. Hypertension.
6. Anemia.
7. Hypocalcemia—hyperphosphatemia—bone disease.
8. Toxic effects of retained drugs.

AZOTEMIA

The normal kidney has a large amount of reserve function for performing its duties. As disease destroys the kidney, this renal reserve is lost. One of the first manifestations is a decrease in the glomerular filtration rate (GFR). As the GFR falls, the plasma levels of nitrogenous waste products (clinically measured as non-protein-nitrogen (NPN) and urea (BUN) levels of blood) gradually rise until the amount being excreted by the kidneys per minute equals that which was being excreted prior to the decrease in the GFR. The levels at which the BUN and NPN stabilize are related to the GFR in an hyperbolic fashion as shown in Figure 1. For a steady state of urea concentration to be reached and maintained, it also follows that the amount of urea excreted by the diseased kidneys must equal the amount of urea produced by the body. Should urea production be increased—for example, increased protein in the diet, internal bleeding and digestion of red blood cells, increased tissue breakdown (eg. infection); and/or GFR be further decreased by continuing renal damage, the BUN will rise further until a new steady state is reached.

ACIDOSIS

The net effect of renal activities serving to eliminate acid from the body is given by the algebraic sum of the urinary excretion of (NH_4^+ + titratable acid − bicarbonate).

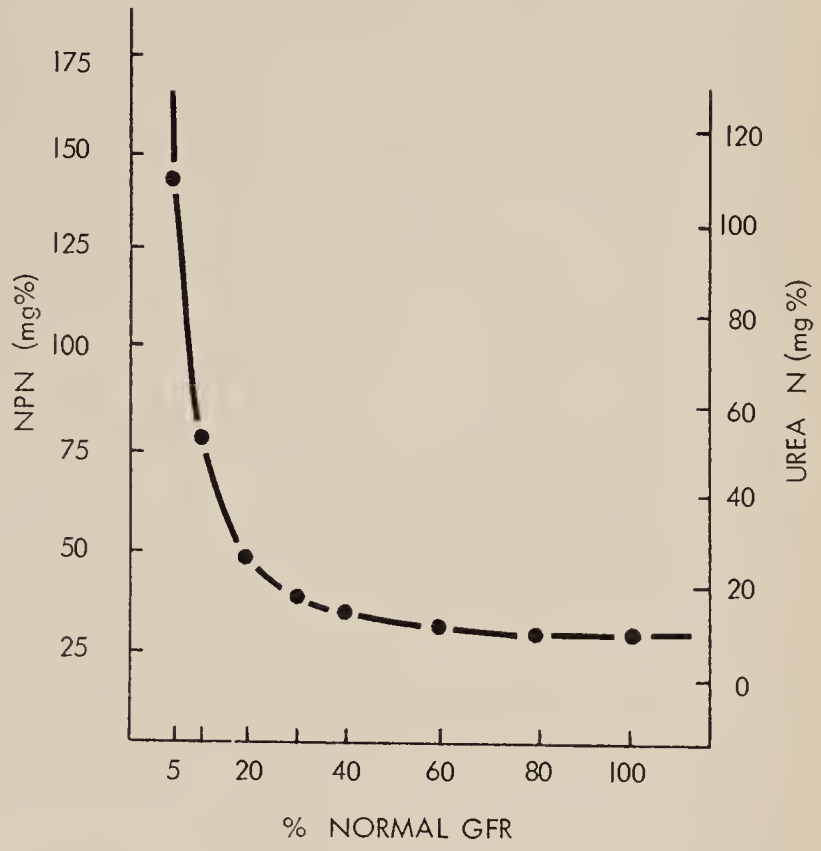

FIG. 1.

As a result of the decline in GFR with advancing renal disease, there is retention of the anions of non-volatile metabolic acids, such as phosphoric, sulfuric, organic acids, etc. It is the anions of certain of these acids, especially phosphate, which act as H^+ ion acceptors in the distal portions of the nephron, enabling the formation of titratable acid. As a result, with the retention of these anions, less H^+ ions will be excreted initially as titratable acid, thus producing a fall in blood pH and causing a metabolic acidosis. But once the concentration of these anions in the blood has reached a level at which their excretion again becomes normal, a steady state will be achieved. At this point, net acid excretion will return towards normal; and this prevents a further increase in the degree of metabolic acidosis.

In addition, the kidney excretes hydrogen ions bound to NH_3 (ie., NH_4^+ ions), in the distal portion of the nephron. Evidence indicates that in chronic renal disease, the excretion of ammonia per nephron is normal or increased. However, because the mass of nephrons is reduced, the total NH_3 excretion is diminished. This factor also contributes to the production of a metabolic acidosis.

Only in a minority of patients does urinary bicarbonate wastage contribute to the acidosis.

DISTURBANCES OF SALT AND WATER BALANCE

Comparatively early in chronic renal disease, the kidneys begin to lose their ability to elaborate a concentrated or dilute urine. The principle reason for this is as follows: as nephrons are destroyed the GFR in the remaining "intact" nephrons increases significantly. This increased GFR per nephron, in addition to the elevation of plasma urea and other solutes due to the overall decrease in GFR, leads to an increased solute or osmotic load per nephron. Under such conditions of osmotic diuresis the ability of the tubules to maximally reabsorb sodium is progressively impaired to the point where eventually urinary sodium excretion and urine volume are relatively fixed by the time that the GFR has fallen to 15 - 20% of normal.

Although in diseases which predominantly affect glomeruli, the tubular function of the remaining nephrons is probably relatively "intact", in diseases in which tubular damage is predominant such as chronic pyelonephritis, phenacetin nephritis, etc., the above described abnormalities may be much more pronounced, and may become evident at a higher GFR.

Thus, if the sodium and fluid intake are less than the obligatory losses, dehydration and sodium depletion may result; whereas, if intake exceeds losses, sodium retention, overhydration, oedema, and congestive heart failure may result.

The defect in sodium conservation by the diseased kidneys is usually mild, and ample sodium is usually provided in the diet to prevent any deficits of sodium in the extracellular fluid of the body. However, if the patient is on a rigid salt-free diet (usually for the treatment of hypertension), a minor negative Na balance may insidiously increase, to produce severe reductions of extracellular volume. In some patients Na deficits may occur because of vomiting and/or diarrhea, disorders which not uncommonly occur in uremic patients. The reduced extracellular volume, caused by the decreased amount of extracellular Na, causes a sharp fall in GFR. As a result, azotemia and acidosis will be increased, and potassium intoxication may develop. Salt loss with continued water intake will lead to dilutional hyponatremia. If water intake is great, water intoxication may ensue because of the decreased ability of the kidneys to excrete a water load.

Unless excessive amounts of Na are ingested, renal retention of Na is usually not a problem. However the administration of salt loads, often as alkalinizing agents to correct acidosis, not uncommonly results in sodium retention, formation of edema, and precipitation of congestive heart failure. Congestive heart failure, secondary to one or more of hypertension, overhydration, or anemia, leads to reduced cardiac output, reduced renal blood flow, reduced GFR, and further retention of salt and water.

HYPERKALEMIA AND HYPOKALEMIA

Potassium balance is usually well maintained by the kidney in azotemic renal failure. Complete reabsorption of filtered potassium probably occurs in the proximal portions of the nephron so that urinary excretion of potassium is entirely derived from tubular secretion of K in exchange for reabsorbed Na in the distal exchange sites.

Severe elevations of serum K (greater than 7 mEq./L) are most frequently found in the terminal stages of renal failure. This is primarily due to the decreased numbers of functioning nephrons which cannot adequately secrete sufficient K in the distal tubules to maintain K balance. There are other factors which may contribute to the hyperkalemia. K loads—for example, by the liberation of large amounts of K from cells as a result of a catabolic response to stress; or in patients with oedema who are given potassium bicarbonate or potassium citrate, instead of the sodium salt, in order to correct acidosis—may produce hyperkalemia. Since the potassium secretory system is functioning near capacity and is critically dependant on sodium reabsorption, any decrease in the sodium reaching the exchange site, such as in salt restriction, could produce K retention. Metabolic acidosis will also increase serum K concentration.

Hypokalemia may result from anorexia, vomiting, diarrhea, or renal potassium wastage.

HYPERTENSION

Almost all patients with chronic renal failure, if not dehydrated, have significant hypertension. The etiological factors of the hypertension are as yet not fully understood. Postulated mechanisms include: increased secretion of renin and hence increased angiotensin production; failure of production of some renal antihypertensive factor; or a combination of both. Overhydration and hypervolemia may constitute a significant additive factor. The hypertension may become symptomatic by producing cardiovascular disease, retinopathy, or encephalopathy.

ANEMIA

The primary cause of the anemia appears to be deficient production of red blood cells in the bone marrow. This failure of erythropoiesis is attributed to the inadequate production of a renal hormone, erythropoietin; and to toxic biochemical effects on the bone marrow, related to the uremic state. A less significant contributing factor is a shortened life span of the red blood cell due to an extracorpuscular hemolytic factor. The hemoglobin concentration may be diminished further by blood loss; and by hemodilution associated with heart failure. The anemia is normocytic and normochromic, unless there is major blood loss, when iron deficiency anemia may appear.

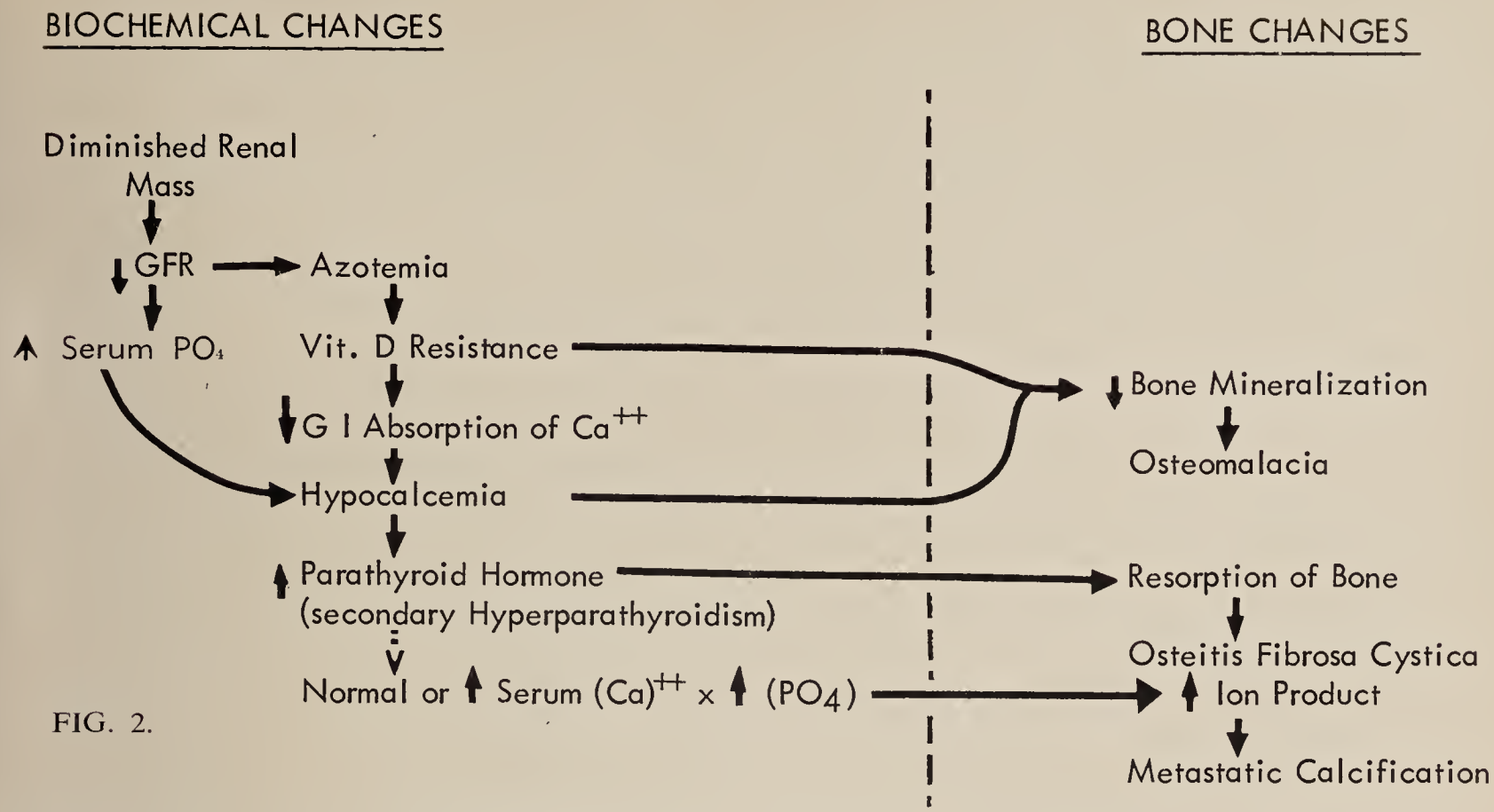

FIG. 2.

HYPOCALCEMIA AND HYPERPHOSPHATEMIA

These states and skeletal disorders are common accompaniments of chronic renal failure. Evidence suggests that the major defect in calcium metabolism is the poor absorption of calcium from the gut associated with a marked resistance to vitamin D. The factors responsible for this resistance are not known. This leads to a negative calcium balance leading to hypocalcemia. The reduced action of Vitamin D also results in decreased bone mineralization producing osteomalacic skeletal changes.

Probably as a result of decreased calcium absorption; and the elevated plasma levels of phosphate, sulfate, citrate and other anions which form calcium complexes, the resulting low plasma concentration of ionized calcium leads to increased production of parathyroid hormone. The latter will cause further removal of calcium salts from bone which may induce the skeletal lesion of osteitis fibrosa cystica.

The serum phosphorus concentration begins to rise when the GFR has fallen to about 25 ml./min. It is the diminished glomerular filtration of plasma P which causes the elevated serum P. There appears to be an inverse relationship between plasma levels of calcium and phosphorus (ie., Caα1/P), such that the elevated levels of plasma P may also be a factor in producing low serum Ca.

Although hypocalcemia usually coexists with hyperphosphatemia, the secondary hyperparathyroidism induced by the initial low values of ionized Ca may be sufficient to raise the serum levels of Ca close to or within the normal range. If this occurs, the mathematical product of the plasma levels of Ca x P may exceed their solubility product, with resultant metastatic calcification. If the osseous disease is mainly due to secondary hyperparathyroidism, the therapeutic administration of Vitamin D, with resultant increase in Ca absorption from the gut, may induce hypercalcemia and metastatic calcification. Figure 2 schematically represents the biochemical and bone changes which may occur in chronic renal failure.

DRUG TOXICITY

Because certain drugs are primarily excreted by the kidney, especially long acting barbiturates and most antibiotics, those drugs which are toxic at elevated serum levels should be given in decreased dosage (eg. kanamycin, colistin, polymixin).

SUMMARY

This article has briefly discussed some of the proposed mechanisms occurring in chronic renal failure which lead to certain alterations in the regulatory and excretory functions of the kidney.

It is hoped that an understanding of the pathophysiology of chronic renal failure will make it easier to comprehend the principles of its management.

ACKNOWLEDGEMENT

Many thanks to Dr. G. de Veber, Toronto Western Hospital, for his aid in the preparation of this article.

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Vesico-Ureteral Reflux As A Predisposing Factor In Urinary Tract Infection

T. F. Long 6T8

INTRODUCTION

There are many factors which predispose to urinary tract infections: congenital anomalies, obstruction, neurogenic disease and renal dysplasia. In recent years another entity has been established as a factor of urinary tract disease—that of vesico-ureteral reflux.

Vesico-ureteral reflux is the reflux of urine from the bladder, through the vesico-ureteral junction into the upper urinary tract. The condition may be readily demonstrated radiologically with the use of a contrast material. After the material has been introduced into the bladder, one or more of several techniques, eg. cystography, voiding cysto-urethrograms or cine fluoroscopy may be used to demonstrate the reflux of dye through the uretero-vesical junction. Reflux is often found in patients with urinary tract infection. Furthermore, in susceptible patients, infection is perpetuated by reflux and chronic pyelonephritis may develop.

This condition manifests itself in both adults and children. The spectrum of clinical findings ranges from cystitis or acute pyelonephritis to those of end-stage chronic renal disease. However, a knowledge of this condition appears to have its greatest application in paediatric cases where it declares itself with the frequent recurrence of urinary tract infections. Hydroureter and hydronephrosis may also be demonstrated in such patients. At this eary stage, corrective, antireflux procedures may be undertaken to reverse the process and preserve renal function.

ANATOMY OF THE URETERO-VESICAL JUNCTION

The urinary tract might best be thought of as having two components; the kidney with its regulatory and excretory functions, and the collecting system: renal pelves, ureters and bladder, which, collectively might be considered as a "reservoir". Intravesical pressure is greater than in other parts of the system, especially during voiding. Normally reflux is prevented by a valve-like action at the vesico-ureteral junction.

The valve has two components: the ureteral—which is of mesodermal origin and the vesical—which is of endodermal origin. Throughout its length, from the renal pelvis down to the ureteral hiatus of the bladder, the ureter is surrounded by smooth muscle which, in general, consists of an inner, longitudinal and outer, circular layer of muscle. However, sectioning and staining reveal some intermingling of these muscle bundles. This arrangement facilitates the peristaltic movement of urine from the kidney to the bladder. In the intravesical component of the ureter there is only longitudinal muscle which is not suited for peristaltic movement and through which the urine flows passively. It is noted microscopically that there is an increase of elastic tissue in this portion of the ureter.

The ureter passes obliquely through the wall of the bladder from the ureteral hiatus on the inferior, posteromedial aspect of the bladder to the ureteral orifice—a distance of 1.5 cm. in the adult. The bladder is lined by transitional epithelium, backed by connective tissue and invested in smooth muscle—the detrussor muscle. Fascicles of this bladder muscle gain attachment to the ureter in its lower 2 - 3 cm. At the hiatus, the detrussor fibres and the ureteral muscle fibres are easily separated. Deep to the detrussor fibres, at the vesico-ureteral junction, there is a small space filled with connective tissue and smooth muscle fibres, which, taken together, has been designated as Waldeyer's Sheath. In the intramural portion of the ureter, proximal to the ureteral orifice, the roof of the sheath splits. The lateral division passes around the ureter toward the floor of the sheath and extends, with the floor, down to the bladder neck to form the lateral aspect of the deep trigone. The medial division of the sheath extends toward its counterpart from the opposite side to form the superior border of the deep trigone. Ureteral tissue beyond the orifice contributes to the superficial trigone. The superficial and deep trigone are not attached but may be difficult to separate.

PHYSIOLOGY

As already indicated, urine is carried by peristaltic waves from the kidney as far as the ureteral hiatus. Then it flows passively through the intramural portion of the ureter and into the bladder. The ureter itself is free at the hiatus and therefore is able to slide back and forth, thereby changing the distance between the hiatus and the ureteral orifice. In its course, the ureter is supported only by the bladder wall.

Intravesical pressure is normally maintained at 7 - 20 cm. of water and rises to a pressure of 50 - 150 cm.

of water during micturition. The vesical neck opens at pressures between 20 and 45 cm. of water. Where the intravesical component of the ureter is normal, reflux probably never occurs despite significant pressure changes in the bladder, such as in the case of vesical neck obstruction. However, where the vesico-ureteral junction is abnormal, reflux may then readily occur with less significant pressure changes.

Electrical stimulation of the trigone has been shown to produce downward movement of the ureteral orifice with apposition of the walls of the intramural ureter. This is also thought to occur during micturition when the muscles of the perineum relax and the detrussor contracts. Sympathetic stimulation and epinephrine are also thought to produce narrowing of the intramural lumen. Following voiding, the external sphincter closes, the detrussor relaxes and the ureteral orifice is pulled upward by the longitudinal muscle of the ureter.

In the intervals between voiding, reflux does not occur as a result not only of the length of the oblique passage of the ureter but its caliber. However, it is the ratio of these dimensions which appears to be the significant factor. A desirable ratio of the caliber to the length is 1 to 5. Finally, the integrity of this "one-way valve" may be enhanced by direct pressure from the filling bladder to produce some narrowing of the ureteral lumen.

PATHOLOGY

As the problem of reflux becomes better understood, it is apparent that reflux may occur in a variety of conditions. Infection however, is a common factor to all of these conditions. Urine provides an excellent medium for the proliferation of bacteria. In patients prone to reflux, contamination of their urine may be complicated by the regurgitation of infected urine, at the time of voiding, through an incompetent "valve" with the subsequent retention of infected urine.

At the present time reflux may be classified according to the following scheme:

I. Primary reflux (developmental trigonal weakness)
II. Secondary reflux due to—
  1. Infravesical obstruction
  2. Neurogenic dysfunction
  3. Inflammation
  4. Iatrogenic causes
III. Reflux due to congenital anomalies

I. Primary reflux

This is the most common type of reflux. However, its aetiology is not entirely clear. It occurs in young children and is ascribed to trigonal weakness. In affected patients, the ureteral orifice is pulled upwards and laterally, possibly due to the unopposed pull of the ureteral longitudinal muscle. In such cases the ureteral orifice lies close to the hiatus. Such children are often plagued by recurrent urinary tract infections in their early years and require tedious prophylactic care. But the characteristic finding in primary reflux has been that such cases may correct themselves at about the age of 12 to 13 years—perhaps as the trigone matures and the strength of its downward pull increases. At this age the intravesical segment of the ureter achieves its adult length of 1.5 cm. and reflux ceases.

II. Secondary reflux

1. Obstruction may occur between the vesical neck and the urethral meatus: eg. meatal stenosis, prostatic hypertrophy or posterior urethral valves. The sustained contraction of the detrussor muscle despite an obstructed outlet, with the consequent rise in intravesical pressure may lead to reflux. With severe vesical contractions, dilatation of the bladder occurs. In addition there may be trabeculation and saccule formation of the bladder wall. These events result in a loss of support for the intravesical portion of the ureter. The ureter, ureteral orifice and even a portion of the trigone may then evaginate through the ureteral hiatus.

2. Neurogenic dysfunction is also associated with reflux. Upper motor neuron lesions, as may be seen in high traumatic paraplegia or multiple sclerosis, are more frequently associated with urinary tract infections due, at least in part, to reflux. On the other hand, lower motor neuron lesions or lesions which interfere with the micturition reflex such as tabes dorsalis are less frequently associated with the reflux. In the former case there is an alteration in bladder tone as well as in the extremities, which may result in bladder changes similar to those seen in infravesical obstruction.

3. Inflammation following infection has been described in the past as both the cause and the effect of reflux. It is now known that reflux of a transient nature may be associated with urinary tract infection but when the infection is suppressed, reflux is no longer demonstrated. It appears that in the presence of infection, the bladder wall becomes oedematous and support for the vesico-ureteral junction is decreased thereby reducing the efficiency of the valve.

However, it should be noted that many people, especially pregnant women, sustain bouts of cystitis without developing reflux. The significant factor appears to be the caliber : length ratio of the intravesical ureter. Where there is borderline competence of the vesico-ureteral valve, (ratio of 1 to 2.5), infection may enhance reflux.

One of the antibacterial defence mechanisms of the bladder is frequent and complete voiding. Reflux enhances the retention of infected urine and bacteria readily proliferate. At this stage pyuria becomes evi-

dent; the common organisms are E. coli, proteus, pseudomonas, staphylococcus and streptococcus fecalis. In long-standing cases of reflux, where the renal parenchyma is subjected to backflow pressures, renal function may remain relatively normal in the absence of infection. However, such a kidney is more readily infected and renal function is subsequently more markedly impaired.

4. Iatrogenic causes of reflux occur following a surgical procedure such as a meatotomy performed to facilitate passage of a calculus or following the excision of a tumour at the vesico-ureteral junction.

III. Reflux due to congenital anomalies

Congenital anomalies such as duplication of the ureters or ectopic orifices are associated with reflux. In such cases there is often a short intravesical ureteral component. The competence of such a vesico-ureteral junction is again reflected by the caliber to length ratio.

CLINICAL FINDINGS

The frequency of urinary tract infections in the population may be considered in reference to four groups:

a. Under 12 years—urinary tract infections are common, especially among girls.

b. 12 to 20 years—urinary tract infections are uncommon.

c. Adults—women are prone to cystitis.

d. Over 60 years—urinary tract infections are more commonly seen in men secondary to prostatic hypertrophy.

The signs and symptoms of reflux may be related to the primary cause, eg. prostatic hypertrophy, or to reflux itself. In young children the only indication of reflux may be the recurrence of urinary tract infections. The signs and symptoms of an acute urinary tract infection are renal pain, chills, fever, nausea and vomiting. Frequency and dysuria may be noted and pyuria may be demonstrated. Specifically, reflux pain may occasionally be described, ie. pain over one or both kidneys when the bladder is full or during voiding and is relieved after voiding. In a few cases patients have presented with chronic renal disease but manifesting only a uremic or hypertensive state.

A patient's chief complaint, on the other hand, may be related to his underlying disease. A person with obstruction may complain of nocturia, frequency, dysuria or colic. Similarly the signs of neurogenic disease may be apparent and reflux may be subsequently demonstrated.

DIAGNOSTIC PROCEDURES

The diagnosis is suggested by the history and physical examination; however an index of suspicion is a valuable asset, especially where children are concerned. But the diagnosis is confirmed by radiological examination.

While the following features of an intravenous pyelogram may suggest the diagnosis, this technique is beneficial in that it also demonstrates renal function:

a. Persistent dilatation of the lower ureter.
b. Areas of dilatation along the ureter.
c. Visualization of the ureter in its full length.
d. Hydroureter and hydronephrosis.
e. Atrophic pyelonephritis, calyectases or cortical thinning.

The best means of establishing the diagnosis is by cystography. Simple cystography may be adequate. However, a delayed or post-voiding cystogram may indicate a larger volume of contrast material within the bladder than is normally seen. The reflux of dye may also be noted. Voiding cinefluroscopy is an ideal method of observing reflux. This, however, requires the co-operation of the patient, which may not be possible. Nevertheless, it is an excellent method of observing the extent of reflux. Cystoscopy is also a useful tool in that trabeculation and saccule formation may be noted as well as an abnormal ureteral orifice. It is important to note that any method may fail on a single examination and it may be necessary to repeat the prócedure.

The severity of the condition and the extent of the renal parenchymal damage may be estimated by the usual renal function tests, ie. urinalysis, BUN, creatinine clearance, concentration tests, PSP, and bacteriological studies.

TREATMENT

Reflux may be managed conservatively or surgically. Where reflux is secondary to some underlying disease or associated with congenital anomalies, the primary problem must be first managed on its own merit, after which reflux may then be treated if necessary.

a. *Conservative management*

The aim of treatment whether it is conservative or surgical, is to preserve renal function and eliminate infection. Primary reflux is the most common type of reflux and in the absence of definite indications for surgery, is best managed conservatively.

Therapeutic measures must be taken to suppress infection. One regimen includes the use of bactericidal drugs for 2 to 3 weeks followed by an antiseptic or bacteriostatic drugs for 6 to 12 months. Frequent and double voiding also aids in the removal of infected urine from the bladder. Urinalysis and bacterial studies should be repeated at frequent intervals. An intravenous pyelogram and cystoscopy should be repeated in a definite period of time, eg. 3 to 6 months. If infection recurs it should be treated vigorously with a cidal antibiotic such as ampicillin, for 2 to 3 weeks.

b. *Surgical management*

Surgery is indicated wherever non-operative measures are inadequate to control infection or where there is progressive renal and urinary tract destruction. Further indications for surgery are as follows:

(i) Abnormal ureteral orifices.
(ii) Ureteral dilatation.
(iii) Hydroureter and hydronephrosis.
(iv) Pyelonephritic changes in the kidney.
(v) Development of a large, thin-walled bladder.

With these indications, an antireflux procedure, ureterovesicoplasty, may be undertaken.

Several procedures have been described but the underlying principle is the same in each technique; the competence of the vesico-ureteral junction, as reflected by the ureteral caliber to intramural length ratio, is decreased due to a short intravesical ureteral component. An attempt is therefore made to create a longer intravesical course for the ureter which will support it as well as possible.

The intravesical component may be increased in several ways. One of these is to create a new oblique passage for the ureter through the bladder wall with dimensions in keeping with the ratio described. The ureter may be pulled down into the bladder wall or the ureteral orifice may be advanced to a new position. Results are best achieved if the re-implantation is confined to the less mobile infravesical component. In higher positions of the bladder, dilatation may produce kinking of the ureter with the development of hydroureter. In any of these procedures, the re-implantation may be complicated by the extent and tortuosity of the ureter. It is also essential that the blood supply to the distal end of the ureter not be compromised.

Following this procedure, a splinting drain from the renal pelvis to the bladder is put in place and a suprapubic cystotomy is done. The drainage tubes are left in place for 7 to 10 days, during which time the patient should be well covered with antibiotics.

RESULTS

Reflux can often be managed conservatively: however, where surgery becomes necessary it can be shown that in good hands, the effectiveness of antireflux procedures may approach 100%. A recent follow-up of patients having undergone antireflux procedures between 1960 and 1962 at the Hospital for Sick Children, bears this out. Forty-three patients with 58 involved ureters were included in the follow-up. The results were assessed with regard to reflux, obstruction, infection and other complications. Of these patients, 54% had good results, ie. no reflux or continuing infection. Those with fair results composed 32%. These patients were, however, infection free when maintained on drugs. Although controlled, a few of these patients had other complications such as persistent hydronephrosis or the development of a diverticulum at the re-implantation site. Six patients were considered to have poor results; of these, 4 had had previous operations and despite antireflux procedures, continued to show signs of infections. Only two cases were ascribed as due to technical failure.

SUMMARY

In the last 10 years vesico-ureteral reflux has been described as a means of perpetuating urinary tract infections—the most serious of which is chronic pyelonephritis. It is a condition which occurs in adults but more commonly in children. Because reflux manifests itself in the childhood years, and with the successful surgical management of this condition, chronic pyelonephritis and other renal damage may be averted.

Reflux is harmful, causing injury to the whole 'reservoir' system. It causes gradual impairment of renal function and enhances the susceptibility to infection. Reflux may be unilateral or bilateral, associated with high or low pressure, transient or constant. It may be transient, ie. initially transient and associated with high pressure, but becoming constant with low pressures.

The condition has variable signs and symptoms as already indicated, but frequently only manifests itself by the recurrence of upper or lower urinary tract infections.

While there are many methods of management, the aim remains the same—to preserve renal function and eliminate infection. The condition may resolve itself with conservative management but surgery may be ultimately necessary. Surgical management has been highly successful.

Urinary tract infections occur with great frequency in the population, particularly amongst children. This condition should be considered in the differential diagnosis of the cause of infection. If the diagnosis is made, medical measures may be undertaken at once and followed by antireflux procedures at a time after the severity of the individual condition has been carefully assessed.

ACKNOWLEDGEMENTS

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Current Status Of Renal Homotransplantation

P. F. Halloran 6T8

The problem of renal homotransplantation, standing as it does as a reprieve from death or chronic dialysis, is a natural target for attention from the popular press. This interest may give rise to unfounded optimism, so that it is desirable that medical personnel be familiar with the theory, applications, and limitations of this procedure.

The aim of this article will be to outline the direction of current research and indicate the possible directions future work may take. It should be appreciated that the literature in this field is burgeoning with new contributions from the immunologist, the urologist, and the internist. Therefore, the reader is encouraged to supplement our review with details from the references.

IMMUNOLOGY

1. The Homograft Rejection Reaction

A homograft or allograft, is a tissue transplanted from one animal to another genetically dissimilar animal of the same species. Mammals possess the ability to reject homografts, beginning at the second half of fetal life (in sheep and in monkey fetuses)[12]. The reaction proceded at a rate roughly inversely proportional to the mass of the organ: renal function in the homotransplant in a previously healthy dog ceases at an average of six days. This is the "first set" reaction, and it confers a specific memory for the antigens in the tissue rejected. Thus, a second graft FROM THE SAME DONOR will be rejected at an accelerated rate—usually by about 24 hrs. This is the "second set" reaction. For obvious reasons, renal homotransplantation in man chiefly encounters a first set reaction.

2. The Antigen

The antigens responsible for homograft rejection, i.e. the histocompatability antigens, are currently being elucidated. They are multiple, are associated with extracellular and intracellular membranes and are lipoproteins. The cell membranes contain the antigens, but the greatest activity is probably between the mitochondrial and microsomal fractions[6].

How the antigens from the donor kidney induce the immune response is unknown, and the role of the macrophage and of the reticulo-endothelial system is uncertain.

However, due to the vascularity of the kidney, it perhaps helps to visualize the donor kidney as a massive dose of intravenous antigens, the most important antigens being vascular antigens.

3. The Immune Response— circulating as cell-bound antibody

The first-set rejection response is usually accepted as being analogous in many respects with tuberculosis-type delayed hypersensitivity which is apparently mediated by antibody bound to lymphocytes. However, some cases of agammaglobulinemia have normal bacterial delayed-type hypersensitivity reactions with abnormal homograft rejection reactions[3]. Yet humoral antibody, while it may facilitate or participate in the graft rejection reaction, does not appear to be essential, since some cases of agammaglobulinemia have virtually normal graft rejection times. As might be surmised, the susceptibility of a graft to cytotoxic antibody varies with the type and quantity of the tissue, a large graft being less easily destroyed than a small graft. In renal transplantation, it has been found that complement component C'2 is depressed three to five days after onset of "threatened rejection" reaction.

In the experimental animal the phenomenon of "enhancement" has been demonstrated in which homograft survival is prolonged by *prior* injection of the killed donor cells into the host. The apparent explanation is that killed cells induce high levels of circulating antibody, which serves to block the reaction between cellular antigens and cell-bound antibody which is necessary for homograft rejection. Evidently, humoral antibody may be either antagonistic or synergistic to the rejection response. This is not currently applicable to human homotransplants.

If the role of humoral antibody is still obscure, the role of cells and cell-bound antibody is somewhat better established. Homograft sensitivity is transferable by lymphocyte injections. In addition, injection of lymphocytes taken from a host (who has rejected a skin graft) into the skin of the donor produces a tuberculin-type delayed hypersensitivity reaction. But it would now appear that subcellular fractions from the sensitized leukocytes are also capable of passively transferring homograft sensitivity.

Evidence that γ-globulin removed from the surfaces of the lymphocytes can do this has been presented, and one case of passive sensitization by RNA derived from sensitized cells has been reported[6].

PATHOLOGY OF THE RENAL HOMOGRAFT REJECTION

In unmodified (i.e. without uremia or immunosuppressive therapy) dogs, the primary or first set rejection response has an early and a late component. The early component is mediated by mononuclear cells in the peritubular capillaries. Damage to these capillaries causes interstitial mononuclear infiltrate and oedema, declining renal function, and ischemic necrosis of proximal convoluted tubule cells. Finally, plugging of larger vessels with fibrin and leukocytes, and polymorph and macrophage invasion of the necrotic tissue is seen.

The late component of the primary rejection reaction is seen in those who survive the earlier reaction, or in humans in whom the earlier reaction is suppressed by immunosuppressives. γ-globulin is deposited in walls of arterioles, causing swelling of endothelium and focal fibrinoid necrosis of the arteriole or glomerular-tuft. This necrotic lesion extends to involve larger arterioles and interlobular arteries. If this acute reaction is reversed, apparently the arterial and arteriolar walls are repaired either completely or by fibrosis, so that intimal fibrosis is a common feature of late homograft rejection reaction.

The pathology of the "second set" reaction involves fibrinoid necrosis of arteries, arterioles and glomerulus, with PCT necrosis and interstitial haemorrhage. It is largely a vascular reaction. Accelerated rejection reactions of this sort have been seen in humans, especially in humans previously sensitized by platelet transfusions[16].

In addition, it should be noted that ABO incompatability in man can mediate failure of the homograft to function. The kidney becomes congested, cyanotic, anuric within hours of transplantation, with marked erythrocyte sludging and interstitial haemorrhage. It will be recalled that ABO antigens have wide tissue distribution outside the R.B.C.

FACTORS AFFECTING THE HOMOGRAFT REJECTION REACTION

A. Degree of genetic similarity

In general, the order of increasing severity of the homograft reaction is: siblings, parents, close relatives, distant relatives and unrelated donors. Attempts to type for histocompatability antigens, or to cross-match donors and recipients, have met with modest success (see below).

B. Host factors

(i) γ-globulin deficiency states: attempts to determine homograft survival time in hypogammaglobulinemia have produced varying results, some cases having greatly prolonged survivals, others only slightly prolonged survivals[6].

(ii) Hodgkins disease: the anergy of Hodgkins disease is unique, occurring at a time when the general health of the victim is good. This contrasts with the anergy of cachetic victims of carcinoma or leukemia. γ-globulin levels are normal. The anergy fluctuates with the level of activity of the disease. Unlike sarcoidosis, the Hodgkins' victim cannot be passively sensitized by injected cells[6].

(iii) Sarcoidosis: prolonged allograft survival, but passive sensitization by injected cells is intact.

(iv) Ataxia telangiectasia: lymph nodes are abnormal, and IgA is reduced, although total γ-globulin levels are normal. The thymus is atrophic, and allograft survival is prolonged.

(v) Uremia: this is the most important anergic state to our discussion, because recipients of renal transplants will be victims of chronic renal disease, in its end stages. The mechanism is obscure.

(vi) Pregnancy: some prolongation of homograft survival[3].

C. Histocompatability testing

Efforts to find a method of predicting compatability by a relatively simple laboratory procedure have not been particularly successful. However, the ideal situation would be to elucidate the chief antigens responsible for the rejection reaction and find donors with antigens compatible with those of the potential recipient.

By analogy with blood transfusion, which is effectively an erythrocyte homograft, we can see that histocompatability testing may take two forms: tests of antigenic similarity (compare blood grouping or "typing"), and test of antigenic dissimilarity (compare "matching" of donor and recipient blood).

(i) *Tests of immunologic similarity*[5]

(a) Leukocyte typing: the leukocytes of an individual may be typed by reactions with standard anti-leukocyte sera obtained from multiparous women, recipients of numerous blood transfusions, and from sensitized human volunteers. The leukocyte undoubtedly carries some of the "histocompatability antigens", but the utility of correctly typing donor and recipient against a panel of antileukocyte sera as above is not established.

(b) Lymphocyte typing: utilizing the cytotoxic effect of a panel of antilymphocyte sera.

(c) Platelet typing: the platelet definitely carries histocompatability antigens strong enough to mediate a "second set" rejection reaction in the kidney of a person previously sensitized with a platelet transfusion[16]. Platelet typing is not currently used.

(d) Erythrocyte typing: of all the major blood groups, only ABO compatability is of proven significance[10]. Rh compatability is usually desirable as well[2].

Thus donor and recipient of a renal transplant should be ABO and Rh compatable.

(e) "Third man" tests: the degree of similarity of the histocompatability antigens of two individuals may be determined in the following way: assume A is to donate a kidney to B. Take a skin graft from A and place it on a randomly selected third person, C. When C has rejected this homografted skin, place a skin graft from B on C. If A is highly similar to B in histocompatability antigens, then the reaction of C to B's tissue will be an accelerated "second set" reaction. If not, the reaction to B's tissue will be a "first set" type. The implication of a second set reaction is that B will accept A's kidney fairly well, because their histocompatability antigens are similar. So far, the utility of this test is not established.

(ii) *Tests of immunologic dissimilarity*

(a) Normal lymphocyte transfer test[10], [5], [4]: lymphocytes from the possible recipient of a renal homotransplant are injected into the skin of possible donors.

Theoretically, the delayed-type hypersensitivity reaction thus produced should be an indication of the ferocity with which the recipient will attack the kidney of the same donor. Unfortunately, the lymphocytes of uremic patients often fail to produce a flare due to the anergy of uremia. Even when the flare appears, it has not been found to be proportional to the severity of the subsequent rejection reaction against the transplant perhaps because of the added humoral factor in the rejection reaction. In short, the test has been found to be qualitative but unfortunately not quantitative in predicting the survival of the graft.

(b) Mixed lymphocyte transformation: when the substance phytohemagglutinin is added to a culture of lymphocytes, it has been empirically found that a large percentage of the lymphocytes will undergo a peculiar transformation into large, blast-like cells with new mitochondria, ribosomes, a Golgi apparatus, and γ-globulin production. The importance of this reaction is that an antigen not present in the person from whom the lymphocytes were cultured will cause a similar transformation in a certain percentage of cells. This reaction has been adapted for histocompatability testing by growing the lymphocytes of donor and recipient in mixed culture. The percentage of lymphocytes transformed should indicate the dissimilarity of the two individuals. A very low percentage will then indicate a favourable prognosis for the subsequent graft. This test has the advantage of being an *in vitro* procedure and more easily quantitated than the NLT test.

SUPPRESSION OF THE HOMOGRAFT REJECTION REACTION

A. Chemotherapeutic agents

The "immunosuppressives" in current clinical use are: cortico-steroids, azathioprine, and Actinomycin-C.

Glucocorticoids act on both the "afferent" and "efferent" limbs of the immune response. They suppress the stimulus to antibody synthesis by decreasing phagocytosis and leucocytic activity. But their immuno-suppressive action is probably most closely related to their suppression of the efferent limb: they decrease antibody synthesis, cause lysis of lymphocytes, and stabilize lysosomes, thereby exerting a non-specific anti-inflammatory action. High dosages of prednisone can reverse a rejection reaction.

Azathioprine is an imidazole derivative of 6-mercaptopurine (6-M.P.). It is reputed to have less bone marrow toxicity but no greater immuno-suppressive action than 6-M.P. 6-M.P. interferes with purine and nucleic acid metabolism in cells synthesizing DNA. It suppresses the primary, but not the secondary ("second set") rejection reaction[14]. It has been shown to triple homograft survival time in rats without impairing wound healing[15]. Lymphocytes from patients treated with azathioprine lose their reaction to phytohemagglutinin, but regain it during rejection crises.

Actinomycin-C is an "antibiotic", produced by a variety of Streptomyces, which attacks DNA to block the synthesis of messenger RNA. Actinomycin-D has been shown to block passive transfer of allograft sensitivity.

Methotrexate and the alkylating agents have not been demonstrated to be effective in blocking homograft rejection reactions in men. However, the periwinkle alkaloids, vincristine and vinblastine, have shown definite promise as immunosuppressive agents, suppressing antibody formation, delayed hypersensitivity, and homograft rejection. They have not currently found clinical application for this purpose.

Chloramphenicol, while not currently used as an immunosuppressive agent, has been shown to have a definite effect in prolonging allograft survival in rabbits. Its action is at the level of the ribosomes, suppressing protein synthesis. However, while it blocks the manifestations of sensitization, it does not prevent large numbers of cells from being sensitized. It has been suggested that this is the mechanism of chloramphenicol-induced aplastic anemia; that many cells become sensitized to chloramphenicol without producing warning signs of mild sensitization. When the drug is withdrawn, the sensitization is then very severe and becomes manifest[9].

B. Irradiation

The use of whole body irradiation for immunosuppression requires a lethal dose for effectiveness. Experimental work involving ablating the bone marrow cells with total body irradiation and injecting bone marrow cells from a graft donor produces a graft vs. host reaction. This is apparently avoided by fetal bone marrow

injection, but such measures have only been useful in the laboratory animal[6-610].

Local X-radiation to the graft site, e.g., 150 rads every two days for three or four doses, has found application in treating rejections.

The possibility of selective irradiation of lymphocytes by a β-emitter located in the right atrium has been raised, and shown to be effective in animals.

C. Ablation Of Portions Of The Lymphopoeitic System

Splenectomy does not prolong graft survival[6-555], but it does prevent the enhancement phenomenon in the laboratory animal. Generally, it is no longer done[1].

Excision of the local lymph nodes, if combined with excision of the graft and if performed within three or four days after grafting will prevent sensitization to the graft tissue antigens. However, this is applicable only to skin grafts, and there is no reason for local lymph node excision in renal transplantation.

Thymectomy is currently under appraisal as a clinical adjunct to renal transplantation. The role of the thymus is not established in the adult. It is known that the thymus is important in early life, and the classical multipore chamber experiments suggest that the thymus in infant mice produces a humoral factor in addition to its "seeding" role. Thymectomy in neonatal mice results in a wasting syndrome at one to three months of age. Thymectomy in the adult mouse results in decreased lymphocytes in peripheral blood, greater ease of maintaining induced tolerance, decreased lymphoid tissue and impaired immune responsiveness.

Depletion of circulating lymphocytes by thoracic duct drainage has produced strikingly prolonged graft survivals in experimental animals.

D. Induced Tolerance

The problem of induction of tolerance in an immunologically competent animal has been studied for some time. Large doses of cell-free antigen preparations given daily over long periods of time can induce tolerance to a graft of tissue containing the antigens, and tolerance may then be maintained by small doses of antigen. This method may some day be applicable to large organs such as kidney, which would maintain the state of induced tolerance by the slow natural release of their own antigens[6-555].

E. Other Available Means Of Altering Homograft Reactions

The use of previous exposure to donor blood to prolong canine renal transplants by the phenomenon of "enhancement" (see above) has met with limited success[6-610].

Immunosuppression with anticomplement (anti-C) agents has shown some usefulness. Investigators used snake venom, which is active against C'3c, a complement component necessary both to phagocytosis and to cytotoxic actions of complement.

Finally, the use of blockade of the reticulo-endothelial system, theoretically to impair phagocytosis by overloading all the phagocytic cells with some substance such as trypan blue, has been attempted experimentally. Unfortunately, it would seem that the allograft itself can stimulate the RE system sufficiently to overcome the blockade.

CURRENT CLINICAL PRACTICES IN RENAL TRANSPLANTATION

The Selection of Recipients

Candidates for renal transplantation should be suffering from end stage chronic renal disease. Commonest diseases in series of renal transplants are, in order: chronic glomerulonephritis, chronic pyelonephritis, and polycystic disease. The lower urinary tract should be normal. There should be no evidence of systemic disease, i.e., one would not transplant for lupus nephritis or the nephritis of polyarteritis nodosa. Candidates are preferably age 35-40 or younger, since this age group has been shown to do better than older persons. There should be no coronory or cerebral artery disease.

Most patients are prepared for transplantation by hemodialysis, as peritoneal dialysis can delay surgery by infection. In addition to azotemia, dialysis corrects hyperkalemic acidosis, hyponatremia, water retention and heart failure so often present when these patients are referred for transplantation.

Digitalis is avoided if possible because of the wide fluctuations in potassium levels, which can precipitate intoxication in patients being dialyzed. The number of dialyses should be kept to a minimum, and azotemia *per se* presents no hazards during anaesthesia.

The usual dietary, fluid and electrolyte, and symptomatic supportive measures are employed.

The Donor Kidney

There are two main sources of kidneys: live donors and cadavers. The use of live donors has the advantages of scheduled operation, shorter ischemic time, better early and late function and longer survivals. The cadaver kidney eliminates the chief ethical problem associated with renal transplantation: subjecting a healthy individual to nephrectomy, with risk of later disease or injury to his good kidney, in order to prolong temporarily the life of another individual.

If a cadaver kidney must be used, the donor should be of middle age or a younger person, who dies suddenly and does not have infection or malignancy and must be free from sepsis, or from a person no older than 70 with normal renal function. The kidney is re-

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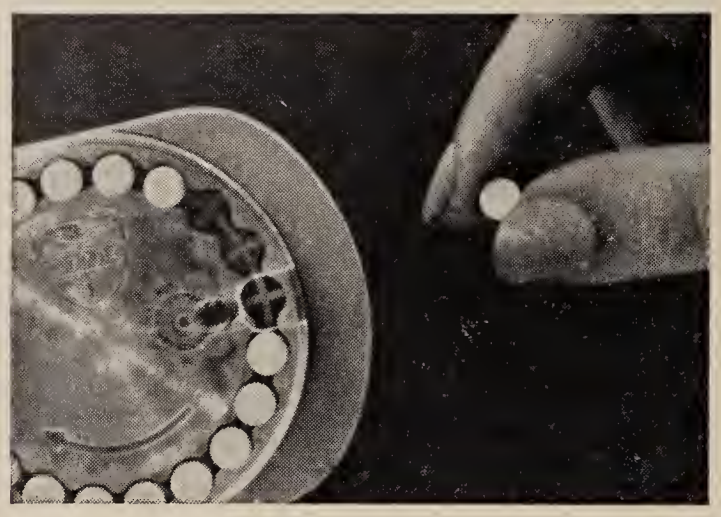

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moved in the Operating Room with full sterile technique. Best results are obtained with kidneys derived from patients whose primary condition was a CVA or head injury.

The kidney is cooled to 10°C and perfused with a solution such as heparinized Ringer's lactate. The addition of procaine may reduce arteriolar constriction due to cold. Hyperbaric oxygen may reduce ischemic damage. Perfusion of the kidneys *in situ* in the cadaver can be accomplished by pumping fluid through the femoral artery, removing it via the femoral vein, and cross clamping the thoracic aorta when such is convenient. The fluid is cooled by passing it through a heat exchanger before re-circulation. However, this is usually not practical or necessary.

In the process of donor nephrectomy, it is desirable to preserve the tissue around the hilus of the kidney, as important blood vessels may pass to supply the ureter through this tissue.

The Transplantation Procedure

Bilateral nephrectomy is usually performed on the recipient of a homotransplant and may be done prior to transplantation. This enables one to follow the function of the graft by the urinary sediment, removes a focus of infection in pyelonephritic patients, and facilitates the control of hypertension.

The possibility of a reduction in the risk of development of glomerulonephritis *in the graft* when this is the primary disease in the host kidneys lends support to removal of the kidneys[16].

Nephrectomy may be delayed until after transplantation in patients receiving cadaver kidneys. However, the method of choice is a one-stage procedure combining nephrectomy with transplantation.

Either kidney may be utilized as a donor organ and generally, it is placed in the right iliac fossa. The renal vein is anastomosed in end-to-side fashion to the external iliac vein. The renal artery is anastomosed end-to-end with the hypogastric artery, and all but the tiniest accessory renal arteries should be anastomosed with branches of the hypogastric artery or local ischemic areas may result. Prolonged ischemic time may result in acute tubular necrosis and an oliguric phase which may last several days.

Finally, the ureter is implanted on the trigone through a submucosal tunnel. The patient's own ureter may be anastomosed to the renal pelvis of the donor kidney. Generally, a urethral catheter is used for a few days[1].

Surgical complications may include failure or thrombosis of the vascular anastomoses, superficial and deep wound infections (usually staphylococcal), necrosis of the ureter or breakdown of the ureteral anastomosis.

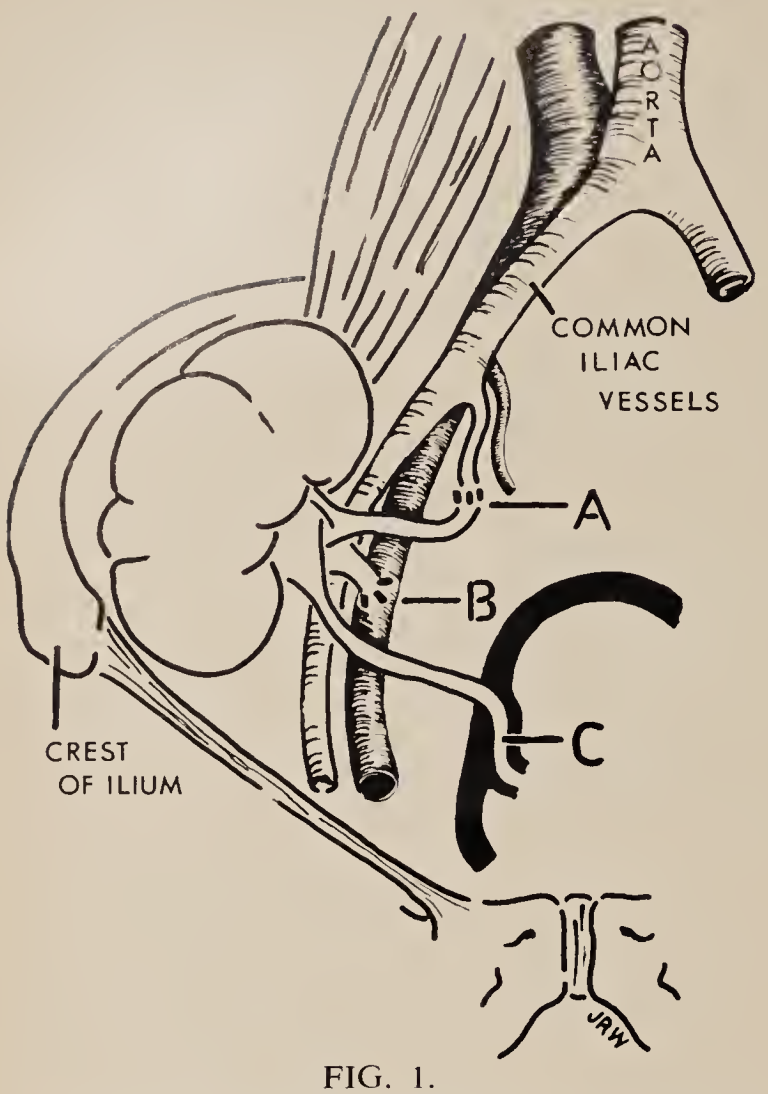

FIG. 1.

Renal Homograft in Position in Iliac Fossa.

A. End-to-end anastomsis of hypogastric artery with renal artery.
B. End-to-side anastomosis of renal vein to external iliac vein.
C. Ureter through muscularis to a submucosal tunnel, opening into bladder through an elevated orifice formed by eversion of ureter.

Splenectomy does not seem to facilitate the control of rejection. The value of thymectomy, if any, is not yet established.

The graft will often begin to function within minutes after re-establishing blood flow. A period of renal shutdown due to acute tubular necrosis accompanies the use of cadaver kidneys more frequently than live kidneys. Post-operative hemodialysis may be necessary. The probability of acute tubular necrosis rises after 45 minutes of ischemia.

THE MANAGEMENT OF THE RENAL TRANSPLANT PATIENT

If the kidney begins to function early, a post-operative diuresis follows which may be profound. The usual practice is to replace the urine output and estimated insensible losses with appropriate intravenous fluids based on the electrolyte composition of the urine.

Coincident with urine output, there will be a remarkable relief of uremic symptoms and a rapid fall in BUN. The post-operative period is marked by improvement in BUN and symptoms of uremia.

Many patients have an episode of rejection in the early post-operative weeks. Prompt diagnosis and treatment can reverse this and subsequent rejections.

The diagnosis of the rejection reaction is mainly based on deteriorating renal function in the homograft, associated with fever, palpable and often tender enlargement of the kidney, and elevated blood pressure. Laboratory data will support the diagnosis: urinalysis reveals round cells ("rejection cells") in the urine. Urine sodium and volume are decreased, while urine osmolality is increased. BUN and serum creatinine rise, clearance declines and proteinuria appears. Serum and urine LDH may be increased. Sequential renal blood flow determinations by I^{131} labelled hippuran may confirm progressive compromise of renal blood supply—however, a retrograde femoral arteriogram will provide more direct and valuable information about the vascular state. Retrograde pyelography may be necessary to distinguish the oliguria of rejection from that which accompanies ureteral obstruction. Incubation of donor platelets with serum from the recipient may reveal impairment of platelet function as based on decreased radioserotonin uptake. The third component of complement, a βIa globulin, is missing on immunoelectrophoresis. A prompt therapeutic response to high dosages of steroids as shown by increased urine output will support the diagnosis of rejection.

The routine for antirejection therapy usually involves azathioprine, prednisone, and actinomycin-C.

Azathioprine is usually begun pre-operatively in relatively low doses (1.5 - 4.0 mg. / Kg. / day p.o.) since the leukocyte count is relatively sensitive at this time. Immediately post-operatively, a leukocytosis resistant to azathioprine occurs, and the dosage may be temporarily increased (5 - 8 mg. / Kg. / day). Thereafter, daily administration at 2.5 - 5.0 mg. / Kg. is initiated and continued indefinitely. Dosage should be reduced if leukopenia appears, and frequent WBC and platelet counts are done. Dosage should be increased during rejection crises.

A difficult situation is apparent when a rejection reaction occurs at a time when the bone marrow is already severely depressed.

Prednisone is valuable in periods of rejection, and in high doses is effective in reversing rejection. Dosages of 150 to 400 mg. per day for a few days are employed, with tapering off of dosage as renal function improves. Prednisone in doses of 10 - 30 mgm./day is commonly used with azathioprine for prolonged periods of time. However, prolonged steroid therapy may be accompanied by increased incidence of upper G.I. haemorrhage, acute and chronic pancreatitis, glycosuria and diabetes requiring as much as 150 units of insulin daily for control, avascular necrosis of the head of the femur, osteoporosis, and Cushingoid facies and habitus.

Actinomycin-C may be routinely administered intermittently I.V. every three to five days in dosages of 200 to 400 micrograms (4 - 8 mgs. / Kg. / day), and may represent a valuable adjunct to steroids and azathioprine in treating acute rejection episodes. Bone marrow depression is uncommon at this dosage level, but mouth ulcers are common.

Supportive medical treatment is essential during rejection crisis. Hypertension is modified with Diuril, reserpine, and Apresoline. Sodium restriction — 200 mg. per day — and fluid restriction is essential to avoid congestive heart failure.

The complications of this profound insult to the organism's metabolic activities are numerous. In early rejection crises particularly, a peculiar wasting syndrome may be seen with diarrhoea, oesophagitis, dermatitis, oral lesions, and profound muscle wasting even in the presence of apparently adequate diet. Leukopenia, with septic complications, and thrombocytopenia, with haemorrhagic complications, may accompany azathioprine toxicity. A peculiar transplantation pneumonitis, marked by fever with gradual onset of cough, cyanosis and hypoxia due to alveolar-capillary block has been described. Hypogammaglobulinemia has been noted during high-dosage steroid therapy and should be treated with gamma globulin if levels fall below 300 mg.%. Hepatitis and hepatic cirrhosis, fungus infections (candidiasis or apergillosis), protozoan infection (pneumocystis carinii pneumonitis), and frequent bacterial infections (staphylococcus, pseudomonas, E. coli and Aerobacter aerogenes) are reported.

GLOMERULONEPHRITIS IN THE TRANSPLANT

The development of glomerulonephritis, usually of the rapidly progressive variety associated with epithelial crescents, has been reported in identical twin transplants and in homotransplants as well. The incidence in homotransplants seems to be related to the genetic similarity of the donor and recipient. The disease usually develops in those whose original disease was glomerulonephritis.

RESULTS OF RENAL TRANSPLANTATION

The Registry of Renal Transplants data in 1966 reports that one can currently expect over 50% of homotransplants involving parents or siblings to survive one year, and 30-50% two years. Cadaver and live unrelated donor one year survivals are currently about 15-20%. Centres experienced in cadaver homotransplants (e.g., Cleveland, Boston, Richmond, Denver, Montreal and Colorado) report survivals of 37% and 67% at one year.

Worthy of note is the improvement over the results reported as recently as 1964, when one-year survivals with sibling kidneys was 39% and with cadaver kidneys 7%.

CONCLUSION

Space does not permit a discussion of heterotransplantation, identical twin transplants, or the ethical problems of homotransplantation. Renal homotransplantation is an experimental procedure, and is undertaken only in end stage disease. Viewed in this light, the recent advances in understanding and controlling immune reactions allow for cautious optimism that renal homotransplantation will continue to improve and eventually be offered as a therapeutic modality.

ACKNOWLEDGEMENT

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The Current Status Of Renal Hypertension

P. B. Tepperman 6T8

I INTRODUCTION

During the last two decades important advances have been made in the understanding of renal hypertension. The purpose of this article is to present a clear picture of this condition and to point out that despite new methods of diagnosis and treatment, the prognosis even in adequately treated cases remains unpredictable.

II ETIOLOGY

The etiology of renal hypertension can be classified as follows:

Parenchymal Causes

1. glomerulonephritis
2. hydronephrosis
3. pyelonephritis
4. perinephritis

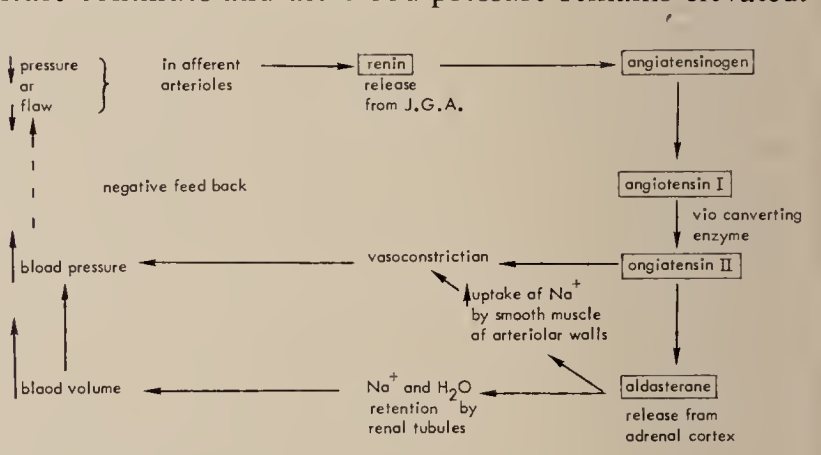
Vascular Causes

1. atherosclerosis
2. fibromuscular hyperplasia
3. Others: a) aneurysm b) inflammatory lesions c) traumatic deformities (including previous surgery) d) congenital or developmental defects eg. kinks, bands.

Of the two groups, renovascular hypertension is much commoner. Regardless of the specific etiology of renovascular hypertension, the common pathological lesion is stenosis of the renal artery or its branches. The commonest cause of stenosis is atherosclerosis. Characteristically, atheromatous lesions are commoner in males, are usually located in the proximal third of the artery and are often unilateral. Fibromuscular hyperplasia, on the other hand, has a strong preponderance for females and is usually found in the middle or terminal third of the main renal artery (and may or may not involve the secondary branches). This lesion is more likely to be bilateral.

III PATHOPHYSIOLOGY

Currently it is thought that a decrease in pulse pressure, mean arterial pressure, or renal blood flow is transmitted via the afferent arterioles to the juxtaglomerular apparatus (JGA) resulting in the release of an enzyme called *renin*. This enzyme acts on an α-2 globulin produced in the liver called *renin substrate (angiotensinogen)* to produce *angiotensin I*, a physiologically inactive decapeptide. Another enzyme formed in the liver, *converting enzyme,* changes angiotensin I to *angiotensin II,* an octapeptide which is a potent vasoconstrictor by itself, but also stimulates the release of *aldosterone* from the zona glomerulosa of the adrenal cortex. This hormone acts on the renal tubules to promote the retention of Na^+ and H_2O (and the excretion of K^+ and H^+), thus increasing the blood volume and pressure. In addition, it causes the transfer of Na^+ into the smooth muscle cells of the arteriolar walls, which some authors feel facilitates a contractile response to vasoconstrictor substances. In a normal person the resultant increase in blood pressure via these mechanisms acts as a feedback to the JGA to inhibit renin release. In cases of decreased flow or pressure through the kidneys, whether resulting from primary *vascular* conditions or from *parenchymal* disease such as interstitial scarring or glomerular proliferation, the feedback mechanism cannot act, renin release continues and the blood pressure remains elevated.



IV DIAGNOSIS

As in any disease state the essentials of diagnosis are a thorough history and physical examination supplemented by laboratory tests and special investigations. Since renal parenchymal hypertension is by and large not cureable by medical or surgical means the following discussion will lay more emphasis on surgically treatable renovascular hypertension.

i) History

Once the existence of hypertension is established the problem resolves itself into deciding whether the hypertension is secondary to an identifiable cause and if so, whether it is surgically cureable or must be managed medically. From the history the following information is important in suggesting hypertension secondary to a renal cause:

a) a family history of hypertension, renal disease, premature atherosclerosis or diabetes.

b) a past history or present symptoms of renal or urinary tract disease.

c) a history of trauma or pain in the region of the kidneys.

The following points in the history, when taken together, are suggestive of unilateral renovascular disease:

a) absence of a family history of hypertension (most hypertension running in families is essential or primary and the absence of a family history therefore makes one suspect the possibility of a secondary cause)

b) absence of past history or present symptoms suggesting renal parenchymal or non-renal causes.

c) sudden onset of severe hypertension in a patient less than 40 or older than 60.

It is important to realize that headache and epistaxis, traditionally regarded as manifestations of hypertension, are no more frequent in hypertensive than normotensive patients. Often the first symptoms are those of heart failure or renal disease.

ii) Physical Examination

The physical signs of renal parenchymal hypertension are for the most part those of renal failure and will not be elucidated here. Virtually the only sign pointing to renovascular hypertension is the presence of a bruit anteriorly over the epigastrium and/or posteriorly in one of the costovertebral angles. Since the bruit is usually low pitched, one should auscultate with the bell of the stethoscope. A bruit in a patient less than 50 suggests renal artery stenosis but in those over 50, it may be caused by atherosclerosis of the abdominal aorta and is less significant.

iii) Laboratory and Special Investigations

After general assessment of the patient including routine blood work, urinalysis, ECG and chest x-ray, non-renal causes of hypertension may have to be ruled out, especially if the history and physical findings are suggestive. One then proceeds with renal function tests such as BUN, serum creatinine, concentration tests, urinary output, intravenous pyelograms (IVP) etc. These are mandatory in all cases of severe hypertension since decreased renal function may either cause hypertension or result from it. When renal hypertension is suspected renal function tests are not necessarily helpful in distinguishing parenchymal from vascular pathology (if indeed by this stage doubt still exists). This is because a decrease in renal function may result from either. In hypertension secondary to parenchymal disease, renal function is almost always compromised but in renal arterial stenosis this is also often the case. If the stenosis is bilateral the GFR may be decreased sufficiently to alter function and when the stenosis is unilateral, the resulting hypertension may cause *nephrosclerosis* (a parenchymal condition) in the contralateral "normal" kidney and thus, decreased function again results. The affected kidney causing the hypertension, because of the stenosis is "protected" from hypertension. As will be seen later, decreased renal function is of great significance in the type of surgical treatment chosen in renovascular hypertension.

If renovascular hypertension is considered likely (which it must if no other cause can be found) there are tests which are of specific diagnostic assistance.

Timed IVP

This differs from a regular IVP in that rapid exposures are taken soon after dye injection (at 1, 2, 3, 5, 10 and 15 minutes). Positive results in this test would include:

a) difference in overall length of the renal shadows (in the preinjection AP film which is routine in all IVP's) of equal to or greater than 1 cm.

b) delay in dye uptake by the parenchyma or in filling of the calyceal system on one side.

c) decreased dye concentration on one side.

I^{131} labelled Hippuran Renogram

This test is used to compare the relative capacities of the two kidneys to take up, concentrate, and excrete radioactive hippuran. Decreased capacity occurs on the affected side.

Split Function Studies

Urine samples from each ureter are obtained by retrograde catheterization and are analyzed for volume, Na^+ and creatinine concentration. Characteristic results in renal artery stenosis are:

a) decreased urine volume and Na^+ concentration from the affected kidney since hypoperfusion leads to decreased GFR and therefore, more time is available for tubular reabsorption of Na^+ and H_2O.

b) increased creatinine concentration from the affected kidney since the tubules do not reabsorb creatinine (even in a normal person) yet reabsorb increased amounts of H_2O.

False negatives *do* result from this test. For example if the stenosis is bilateral or if there is only a small segmental arterial lesion, the two samples may not differ appreciably.

If the above three tests indicate renovascular disease then a *renal arteriogram* is obtained to confirm the diagnosis and as a guide to the type of operative procedure required. Two other tests can be used if available:

Urea Washout Pyelogram

This is usually done in conjunction with a timed IVP. Immediately after the latter, urea is injected. This substance, an osmotic diuretic, "flushes" out the dye from the kidneys more rapidly than normal. In arterial

stenosis the dye is flushed out more slowly from the affected side and thus will appear more concentrated, longer.

Renin Assays

These may be obtained from renal or peripheral venous blood and ideally, in renal artery stenosis, levels should be elevated.

V TREATMENT

In the past decade the trend in renovascular stenosis has been away from nephrectomy and toward conservation of renal tissue by arterial reconstruction. Nephrectomy of the affected kidney is usually not the treatment of choice for two reasons. Firstly, it is protected from nephrosclerosis by the stenosis and so may function very well with arterial reconstruction. Secondly, if it is removed and the other kidney has nephrosclerosis, then renal failure is the likely result. Thus, the reason for evaluation of both kidneys separately becomes clear. Usually the patient with unilateral stenosis and a healthy contralateral kidney does not exhibit renal insufficiency.

The two commonest procedures for vascular reconstruction are bypass graft and endarterectomy with patch graft angioplasty. Nephrectomy is indicated if arterial reconstruction is not possible or if there is unilateral *parenchymal* disease, provided in both cases that the contralateral kidney is healthy.

VI PROGNOSIS

Debakey[1] and his group have reported on two groups of patients with excellent results in both series. Prior to May 1964, he reported that of 432 patients treated surgically, 81% had significant improvement and 41% of these were cured. Since then, of 195 patients, 86% exhibited a favourable response and 57% of these were cured.

Kirkendall et al[2] in a more recent review, however, reported on 2000 patients evaluated for hypertension. From this group 50 were treated surgically and he claimed improvement in only 48% of cases with an 18% cure rate.

This variability in results is observed again and again and well illustrates the controversy at present over the efficacy of surgical treatment of renovascular hypertension.

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Fundamentals Of Radiologic Examination

Skull Films

INTRODUCTION

In past years the undergraduate medical curriculum of this university has not laid much formal emphasis on the subject of radiology. The result has been that most medical students and indeed, many graduates, never learn the essentials of radiological examination and are often unable to assess even the most routine x-ray. This situation is partially understandable in light of the vast body of basic knowledge that must be mastered at the undergraduate level. The deficiency has been recognized however, and beginning in 1969, radiology will receive more intensive coverage in the curriculum. This will be accomplished at both the preclinical and clinical level. Radiographic anatomy, pathology, and also radiological demonstration of physiological principles will be correlated with the courses in gross anatomy, pathology, and physiology. Later, radiologic results will also be correlated with the clinical work in respect to all patients. In addition, a regular fourth year rotation on radiology will be part of the curriculum.

In the investigative armamentarium available to the physician today, there is probably no diagnostic tool more frequently of assistance than radiography. This is not to suggest that a thorough clinical assessment of the patient is not mandatory, but it is a fact that the only time a doctor can actually "see" inside his patient is through the medium of x-ray. Many conditions, most notably, some malignancies, are without symptoms and signs until inrreversible damage, and even death, are inevitable. Radiologic techniques are often the only means of finding these lesions while they are still curable. This applies to virtually all branches of clinical medicine, and every physician, from the junior intern to the specialist, must be able to accurately evaluate x-ray films.

It was with this in mind then, that this feature was conceived. In previous journals, features on radiology have appeared, usually consisting of sample pathologic x-rays which the reader was to attempt to diagnose. This year, the format will be different and we hope, more instructive, as well as interesting. The important concepts required to read the films commonly encountered in clinical practice will be outlined, with emphasis on a *systematic* method of examination. In addition, normal x-rays will be presented together with pathologic examples so that the reader may test his diagnostic skill. Skeletal radiology is beyond the scope of this feature and so, with the exception of the issue dealing with skull films, fractures, rheumatology, etc. will be omitted and emphasis will be on visceral radiology. The subjects to be covered are as follows:

1. November—Skull films

2. December—The Chest—part one—Lungs, Pleura, Diaphragm

3. January—The Chest—part two—Heart and Great Vessels

4. February—The Abdomen—part one—Gastrointestinal System

5. March—The Abdomen—part two—Urinary System

6. April—Special Techniques

THE SKULL

Routine Skull Films

Four views are routinely taken:

1. Lateral view—Figs. 1A and 1B.

2. Postero-anterior (PA or Caldwell) view—Figs. 2A and 2B.

3. Fronto-occipital (Towne) view—Figs. 3A and 3B.

4. Submento-vertical (Basal) view—Figs. 4A and 4B.

The "A" views in each case are numbered to show the *normal* anatomical features. The numbers correspond to descriptions in the text and to the labels of the diagrams. It is suggested that the reader examine the *abnormal* "B" films before consulting the case histories and diagnoses. This practice should be employed in reading future issues as well.

Before proceeding further, the reader should understand two important technical concepts. Firstly, by convention the first letter of an x-ray requisition refers to that part of the patient closest to the beam (not the film) and therefore, best visualized. Thus, a PA view of the skull has the nose and forehead touching the film, and the central ray of the beam entering the skull just below the external occipital protuberance. Similarly, if disease is suspected in the right lung, a *right* lateral x-ray should be specified. Also, regarding the density and the thickness of structures seen on x-ray, those which are more dense or thick show up as white shadows and are called *radioopaque*. Bone is radioopaque. There are both thick and thin areas of bone in the skull. The thin bone is less radioopaque than the thick bone. At the opposite end of the scale, the least dense and thinnest areas appear black and are referred to as *radiolucent*. For example, air whether in the lungs or in the ventricles of the brain, appears black.

FIG. 1.

(A) Normal adult skull — lateral view. 1 - Anterior border of middle fossa; 2 - Anterior clinoid process; 3 - Sella turcica; 4 - Posterior clinoid process; 5 - Mastoid air cells; 6 - Calcified pineal gland; 7 - Sphenoid sinus, 8 - Frontal sinus; 9 - Lambdoidal suture; 10 - Coronal suture; 11 - Middle meningeal artery groove; 12 - Posterior fossa.

(B) Unknown 1 (see text of article).

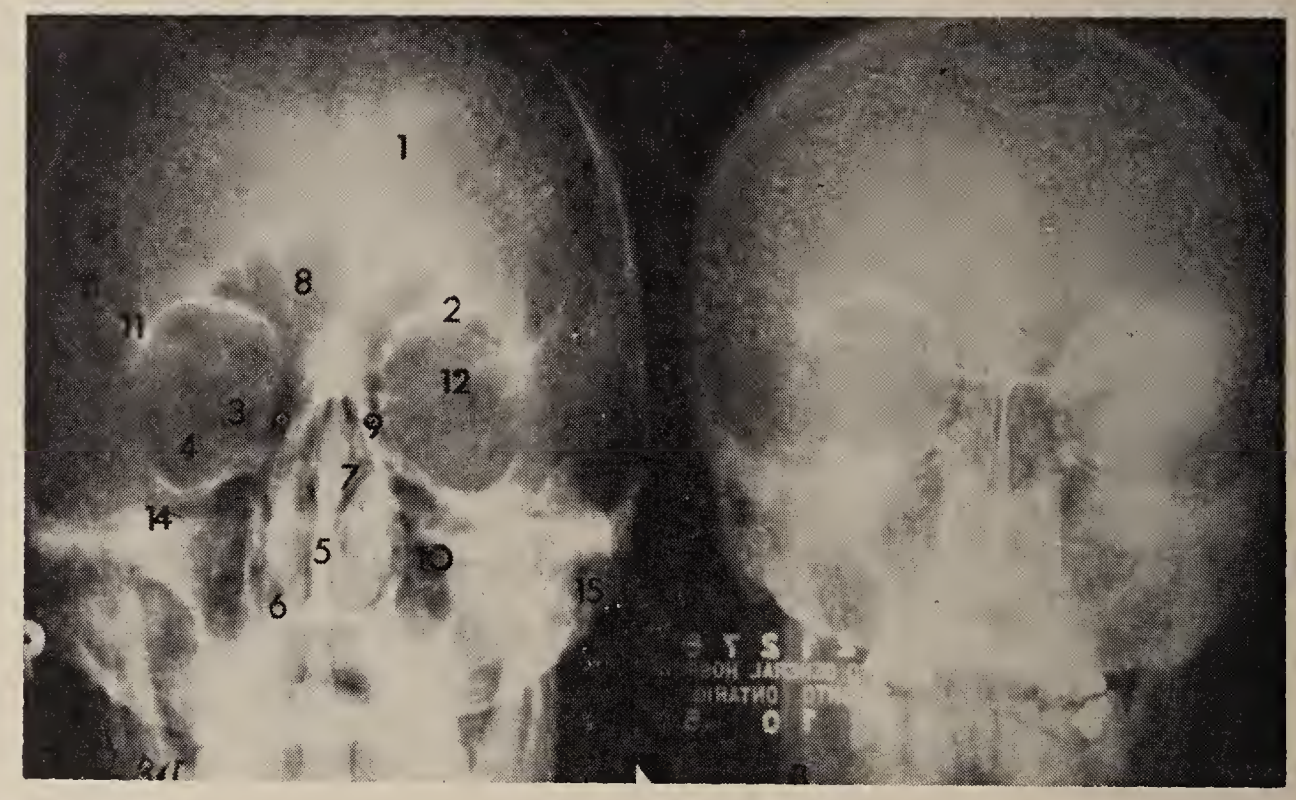

FIG. 2.

(A) Normal Adult Skull — postero-anterior (Caldwell) view. 1 - Frontal bone; 2 - Supra-orbital ridge; 3 - Superior orbital fissure; 4 - Orbit; 5 - Nasal Septum; 6 - Inferior concha; 7 - Superior concha; 8 - Frontal sinus; 9 - Ethmoid sinus; 10 - Maxillary sinus; 11 - Sphenoid ridge; 12 - Lesser wing of sphenoid; 13 - Sagittal suture (top of skull in midline—not shown); 14 - Petrous ridge; 15 - Mastoid cells.

(B) Unknown 2 (see text of article).

Method of Examination

As mentioned previously, *systematic* examination of all films is the secret of successful x-ray reading. The system used does not matter but in skull films the following sequence is usual:

1. The soft tissues
2. The skull—size, shape, symmetry
3. The bones—thickness and density
4. The sutures and vascular markings
5. The base of the skull and orbits
6. Intracranial calcifications
7. The mastoid air cells and paranasal sinuses.

1. *The Soft Tissues*

These are examined under bright light (not on the viewbox) and the most useful views are the lateral and Towne. Localized swelling may pinpoint the site of trauma or fracture, or may represent an abscess with underlying osteomyelitis.

2. *The Skull—size, shape, symmetry*

Considerable variation exists in the size and shape of normal skulls. In adults the facial area is approximately half the area of the cranium ("cranium" refers to that portion of the skull excluding the facial bones), whereas in children it is less than half. With respect to shape, the normal skull is referred to as mesaticephalic. Long, narrow skulls are called dolichocephalic and short, broad skulls, brachycephalic. Symmetry is extremely important in radiology when examining any "bilateral" structure such as the skull, and when it is lacking a lesion must be suspected. The basal, PA, and Towne views are all useful to effectively examine for symmetry.

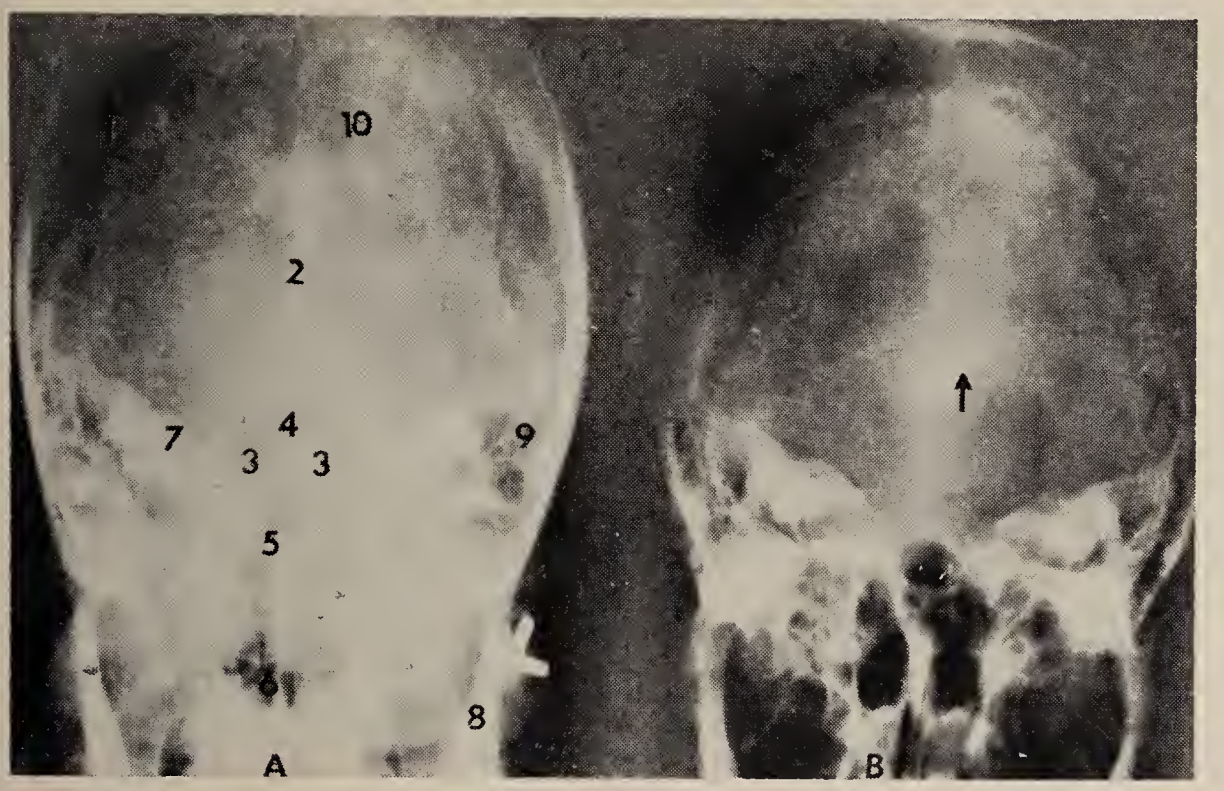

FIG. 3.

(A) Normal adult skull - Towne (fronto-occipital) view. 1 - Lambdoidal suture; 2 - Calcified pineal; 3 - Post. clinoid process; 4 - Foramen magnum; 5 - Sphenoid and ethmoid sinuses; 6 - Nasopharynx; 7 - Petrous ridge; 8 - Mandible; 9 - Mastoid air cells; 10 - Cerebral fossa.

(B) Unknown 3 (see text).

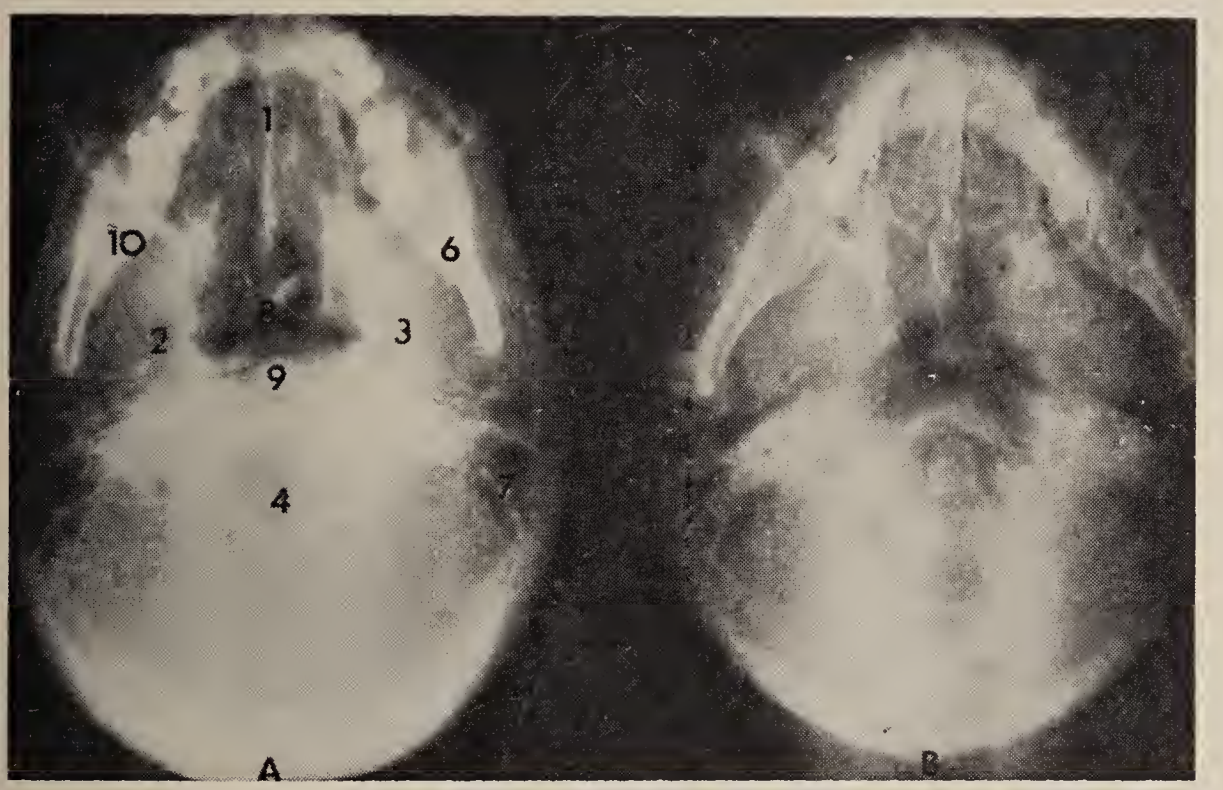

FIG. 4.

(A) Normal adult skull - basal (submento-vertex) view. 1 - Nasal septum; 2 - Foramen ovale; 3 - Foramen spinosum; 4 - Foramen magnum; 5 - Maxillary sinus; 6 - Mandible; 7 - Mastoid air cells; 8 - Nasopharynx; 9 - Arch of 1st cervical rib; 10 - Anterior border of middle fossa.

(B) Unknown 4 (see text).

3. *The Bones—thickness and density*

Normal variation also exists in the thickness and density of the cranial bones. Cranial bones in the negro are thicker than in whites. Also, in any one skull the most consistently radiolucent area is the temporal region because the bone there is thin. Some examples of pathological variation in thickness and density follow.

a) Thickening
   (i) generalized: acromegaly, sickle cell anaemia, pseudo-hypoparathyroidism, Paget's disease, fibrous dysplasia.
   (ii) localized: hyperostosis frontalis interna, over a meningioma

b) Thinning
   (i) generalized: osseous defects representing destruction by benign or malignant neoplasms
   (ii) localized: superficial intracranial tumours, subdural hematomas or hygromas, multiple myeloma

c) Increased Density—osteopetrosis (particularly at the base of the skull)

d) Decreased Density—osteoporosis (again, particularly at the base in the region of the sella turcica so that it may be difficult to explain the decreased density on the basis of increased intracranial pressure or simple osteoporosis).

4. *Sutures and Vascular Markings*

Normal sutures in an adult are surrounded by a narrow area of increased density. This is important in

distinguishing them from fractures, in addition to the typical anatomic location and digitations seen in a suture. Suture width in growing individuals may also be significant (more than 2 mm. in individuals from 3 to 16 years indicates either increased intracranial pressure or traumatic diastasis).

The vascular markings are usually best seen on the lateral projections. The meningeal vessels produce grooves as they course along the surface of the dura. These grooves branch and are not as radiolucent as fracture lines (since they do not involve the full thickness of the bone). The relative size of these arterial grooves should be noted. If one of the branches of the middle meningeal artery produces a wider groove than other adjacent branches, the possibility of an abnormal increase in blood flow through this branch should be suspected. This is commonly due to a meningioma, in which the middle meningeal flow is greatly increased to supply the very vascular tumor.

5. *Intracranial Calcifications*

Some calcifications are normal while others are pathologic. Normal calcification may be seen in the pineal gland (in lateral and Towne views), in the dura mater (especially the falx and tentorium), in the petroclinoid ligaments, in the habenular commissure, and in choroid plexuses. Pineal gland calcification is extremely useful when a space-occupying lesion is suspected since, being a midline structure, it may be displaced to one side on the Towne projection (deviation of more than 2 mm. from the midline is significant).

All other calcification is pathologic and is commonly seen in diseased arteries (atherosclerosis), pituitary adenomas, sub-dural haematomas, arteriovenous malformations, brain abscesses, gliomas, tuberous sclerosis, and teratomas.

6. *The Base of the Skull and Orbits*

a) Sella Turcica

This is best seen on the lateral films. Its contour is usually distinct and smooth, and sometimes a "double contour" is seen in which two lines appear very close together. This is caused by slight depression of the sella by the pituitary gland and is normal. Enlargement of the sella turcica is very significant and accurate means of measuring it have been devised.

(i) Linear Measurements

The greatest AP diameter (from the lateral view) of the fossa is 17 mm. and the greatest vertical diameter is 13 mm. The latter is measured from the lowest point in the fossa to a horizontal line extending from the top of the dorsum sellae to the tuberculum sellae. The width of the sella may sometimes be ascertained from the Towne view and it varies from 10-15 mm.

(ii) Volume Calculations

This is obtained by using the formula: Volume = ½ (length x depth x width). The mean volume is 594 $mm.^3$ with the normal range from 240 - 1092 $mm.^3$ The regularity of the margins of the sella is also important (irregularity likely denotes disease). The clinoid processes should always be examined for erosion, which may result from tumour or increased intracranial pressure.

b) Middle Cranial Fossa

This fossa and its borders should be examined for changes in size, shape, and symmetry on both lateral and basal views. The anterior border is demarcated by a sharply defined, curvilinear line. The floor of the middle fossa is formed by the greater wing of the sphenoid on each side.

c) Orbits

On the PA film, the upper portion of the orbit presents three roughly horizontal lines from above downward.

1. The superior border of the orbit (supra-orbital ridge).

2. The roof of the orbit which describes a curvilinear shadow concave downward.

3. The line formed by the posterior portion of the frontal bone, and the wings of the sphenoid. The sphenoid ridge refers to the lesser wing, and the superior orbital fissure is situated between the lesser and greater wings.

These structures should be examined for symmetry, shape, and in particular, texture.

d) Petrous Ridge (Towne and PA views)

This ridge is the superior border of the petrous bone and is pyramidal in shape. The border is not straight but is slightly undulated. The pyramids must be examined to detect the presence of enlargement or erosion of the petrous borders, and to detect destruction in the region of the middle ear and jugular foramen. The internal acoustic canal must be examined very carefully to detect erosion due to a tumor of the eighth cranial nerve (acoustic neuroma).

e) Foramen Magnum

Destruction of the foramen can be well seen on basal and PA projections. In addition, a view is obtained of the approximate relationship of the atlas together with the odontoid process (of the axis), and the foramen.

7. *Mastoid Air Cells and Paranasal Sinuses*

a) Mastoid Air Cells

Special *oblique-lateral,* and either *AP or PA views of both mastoids* are the minimal requirements for a

mastoid study. Additional views are afforded by the routine PA and basal skull films.

Normally the mastoid cells are well aerated (radiolucent). In acute mastoiditis, haziness or "clouding" associated with loss of the sharply demarcated individual air cell walls occurs. On the other hand, thickening of the air cell walls and even complete sclerosis is evidence of chronic inflammatory disease.

b) Paranasal Sinuses

The paranasal sinuses—maxillary, frontal, ethmoid and sphenoid—should also be examined on all views for "clouding". This may be due to neoplasm, inflammation with edema, or hemorrhage. The characteristic finding in inflammatory disease is increased thickness of the lining membrane of the sinus. The inflammatory process (sinusitis) may or may not be associated with a fluid level (showing a flat superior border). Another important abnormality of the sinus is disappearance of the muco-periosteal junction and demineralization of adjacent bone. This occurs when infection extends beyond the membrane into bone and also when bone is eroded by a neoplasm originating in the sinus.

CASE HISTORIES

The reader should now have decided for himself what the radiographic lesion is in each of the pathologic "B" x-rays and should be thinking of possible pathologic lesions to account for them.

Case I (Fig. 1B)

A 29-year old male presented with a 9-year history of severe headaches and bilateral blurred vision. Physical findings included obesity, female hair distribution, and bilateral optic atrophy. The diagnosis should be obvious! On x-ray, enormous enlargement of the pituitary fossa and erosion of the base of the sphenoid is easily seen. At operation the preoperative diagnosis of pituitary tumour (chromophobe adenoma) was confirmed.

Case 2 (Fig. 2B)

A 40-year old female gradually developed bilateral blurred vision and deafness over a 5-year period. The only significant physical finding was papilledema. There is an obvious sclerosing lesion in or behind the left orbit. You will notice that the lesser wing and ridge of the sphenoid would seem to be obliterated in Fig. 2B but lateral films would be necessary to positively localize the AP depth of the lesion. The final diagnosis in this case was meningioma at the tip of the temporal lobe eroding into the lesser wing and ridge of the sphenoid.

Case 3 (Fig. 3B)

This 36-year old man presented with bifrontal headaches of 2 years duration. He had also noticed numbness of the left lower face and bilateral blurred vision. The Towne view reveals that the calcified pineal gland is shifted 10 mm. to the left. At autopsy, the space-expanding lesion was proven to be a meningioma of the Falx cerebri.

Case 4 (Fig. 4B)

A 47-year old man complained of headaches and vomiting for seven weeks. He was ataxic and noted to have a right lateral gaze with left facial weakness of the lower motor neuron type. The x-ray reveals a striking lack of symmetry in the position of the anterior border of the middle cranial fossa (outlined by the broken line). Is the border too far anterior on the right or too far posterior on the left? A glance at the normal will confirm your suspicion that the right is too far anterior. At operation a large arachnoid cyst was discovered and evacuated.

Z. Cohen 6T9

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Medical Muses

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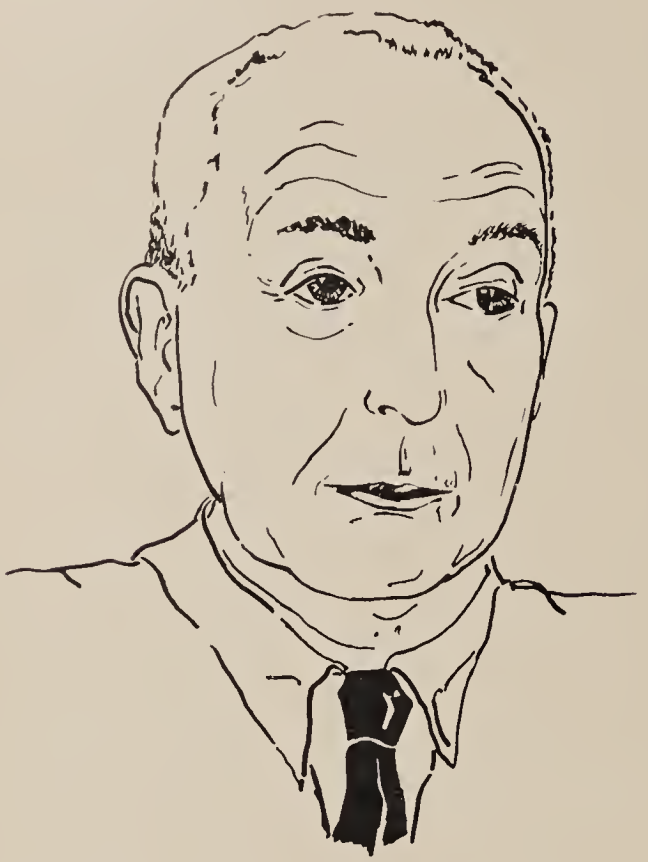
Canadian-born Urologist Wins Nobel Prize in Medicine and Physiology



In October 1966, it was announced that Charles Huggins, Urologist and Peyton Rous, Cancer Researcher, were the 1966 Nobel Laureates. This was indeed an important occasion since no Nobel Prize had hitherto been awarded as recognition for the investigation and treatment of neoplastic disease. The work for which this award was given dealt not only with the nature of malignancy but also the effective measures to combat the tragic consequences of the disease in man. Such was Charles Huggins' contribution when he helped to revolutionize the approaches to the treatment of carcinoma of the prostate.

Charles Huggins, now director of the Ben May Laboratory for Cancer Research at the University of Chicago, was born in Halifax, Nova Scotia, in 1901 (the year of the very first Nobel Award) and was educated at Acadia University, Nova Scotia and Harvard Medical School. After a surgical apprenticeship at the University of Michigan, he joined the Medical School of the University of Chicago, as one of its original members, where he has been for forty years. He entered the field of urology and was appointed the Head of the Urological Division of the Department of Surgery. In 1930 he was sent to Europe for clinical urological training and it was there that he gained his background in phosphatases which were the corner stones for his future work in the investigation of neoplastic disease.

His background in urology gave Huggins the basis for his studies in the physiology and biochemistry of the male urogenital system, in particular the chemistry and hormonal control of the male accessory glands of reproduction. By an ingenious operation he was able to separate the prostate gland of dogs from the urinary tract and was thus able to study the output and biochemistry of prostate secretions. This paved the way for further studies into the hormonal control of prostate growth and function, which showed the inhibitory effects of these processes by estrogens. In his classic paper (Science, June 18, 1943) "Endocrine control of Prostate Cancer", he stated:

"It is possible, by reducing the amount of activity of circulating androgens, to control, more or less, far advanced prostate cancer in large numbers of patients. In this case the androgen control seriously disturbs the enzyme mosaic of the cancer cell, at least with respect to the important energy producing protein catalysts, the phosphatases."

He was able to use increased serum phosphatase levels as an important diagnostic test for carcinoma of the prostate. But not only were these levels decreased by castration and estrogen treatment, there was also an accompanying increase in appetite and relief of pain within days after initiation of treatment, as well as a decrease in size of the neoplasm. Thus he had laid the ground work for a rational treatment of a tragic disease.

Huggins was one of the first people to use diethylstilboestrol in lieu of castration, however it proved to be less effective than surgical techniques. The surgical results showed patients to be 25% cancer free after seven years, while the female hormone treatment was only temporarily effective in a limited number of cases. Nevertheless the outstanding feature of this therapy was that this was the first non-toxic agent of known chemical composition to be recognized as an ameliorator of wide-spread carcinomatosis in man. This stimulated subsequent developments in anti-neoplastic chemotherapy and led Huggins to propose that carcinoma is not always autonomous and self-perpetuating, but that it may be sustained by secretions which are apparently normal in kind and rate.

Another observation which Huggins made during these studies was that the urinary excretion of steroids in patients with carcinoma of the prostate, which was comparable to normals before orchectomy, fell after the operation but rose again, to higher than preoperative

levels. He attributed this to increased adrenocortical function and proposed that the limited value of anti-androgenic therapy might be due to production by the adrenal cortex, of sufficient quantities of growth promoting steroids to maintain the prostatic carcinoma. To counteract this, Huggins performed an adrenalectomy, and with the introduction of corticoid replacement therapy, was able to help 50% of patients so treated.

Carrying on in this vein, Huggins turned his attention to carcinoma of the breast. In this field he was able to show that bilateral adrenalectomy, in conjunction with ovarectomy, provided relief in some 30 - 40% of patients with metastatic carcinoma of the mammary gland.

In recent years Huggins has been studying carcinogenic agents such as 7-12 dimethyl benzathracene, which he showed could induce hormone dependent tumours in selected strains of female rats. He has suggested that carcinogenic molecules (known as polynuclear hydrocarbons) masquerade as hormones or hereditary material and as such enter the cell and induce malignancy in it.

One noteworthy point is Dr. Huggins' stand on the carcinogenic effect of oral contraceptive pills. He stated in 1964, that the data collected from thousands of female patients indicated that the pills are *not* primary etiologic factors in the development of malignancy.

Charles Huggins has been awarded the Nobel Prize for work that shows his great ability to use the scientific method both at the bedside and in the laboratory. This talent has enabled him to make great contributions to the world of healing and to truly aid in the relief of human suffering.

Miss P. Kirkpatrick 6T9

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Erythropoietin

INTRODUCTION

The regulation of erythropoiesis has interested researchers for many years. Added impetus has recently been provided by the elucidation of the substance *erythropoietin* as the key to a relatively simple homeostatic feed-back system regulating red blood cell production that, theoretically at least, is well suited to laboratory investigative procedures. Much of the current interest in the subject centres around the role of erythropoietin in the anemia of chronic renal failure. This brief communication will outline the current thoughts regarding this hormone, and comment will be made on the clinical application of this knowledge.

HISTORY

The increased concentration of hemoglobin in animals raised at high levels of altitude prompted Meischer in 1891 to postulate that erythropoiesis was regulated directly by the level of oxygenation within the bone marrow. Soon thereafter, Carnot and DeFlandre injected serum from anemic rabbits into normal animals and found the recipients' red blood cell count to be nearly doubled. They postulated that a potent plasma factor (hémopoiétine) was elaborated in response to hypoxia or anemia, and that this was capable of directly stimulating erythropoiesis.

It was not until 1950 that Reisman reconfirmed the presence of such a factor. He connected two parabiotic rats by a surgical anastamosis between skin and subcutaneous tissue. One received an 8% oxygen hypoxic atmosphere, the other normal room air. Although one only had arterial desaturation, it was found after 5 weeks that both partners developed polycythemia and erythroid hyperplasia of bone marrow.

A woman with a patent ductus arteriosus with reversed blood flow through the shunt, was described by Stohlman *et al* in 1954. Fully oxygenated blood was received by the upper part of the body including sternal bone marrow, while subdiaphragmatic areas, including the iliac marrow where perfused by desaturated blood. Iliac and sternal bone marrow studies revealed red cell hyperplasia in *both* sites, indicating that marrow anoxia was not a prerequisite for increased erythropoiesis and that the likely anatomical source in man for this humoral factor is subdiaphragmatic.

PROPERTIES OF ERYTHROPOIETIN

Although not fully purified, erythropoietin appears to be a non-dialyzable, heat-stable glycoprotein of molecular weight approximating 30,000, and with the electrophoretic mobility of an α-globulin. It is weakly antigenic and specific anti-erythropoietin antibodies have been prepared.

Assay methods are as yet inaccurate, being insensitive to low levels of activity. Bio-assay is obtained by quantitation of erythropoietic responses in animals whose bone marrow has been suppressed by hypertransfusion, hypophysectomy, starvation, or induction by anoxia of secondary polycythemia. Parameters of response most commonly used are an increase in reticulocyte count and/or an increase in plasma disappearance time of radioactive iron. More recently immunoassay has been developed using specific erythropoietin-inhibiting antisera.

MECHANISM OF ACTION

The site of action of erythropoietin appears to be the pronormoblast—the earliest precursor cell in the erythroid compartment. Apparently this cell is capable of storing information imparted to it by erythropoietin to the effect that it must wait until a critical level of totipotential stem cells have regenerated (to safeguard against their depopulation) before it may proceed with normal differentiation to the more mature stages. The precise mechanism of this action is unknown, although Stohlman and others believe erythropoietin may somehow involve induction of enzymes concerned with hemoglobin synthesis.

SITES OF ACTION OF ERYTHROPOIETIN

The study of the reverse PDA syndrome alluded to above suggested a subdiaphragmatic origin of erythropoietin. It is now well known that following bilateral nephrectomy, activity falls to low levels. Also, a significant increase in erythropoietin in the renal vein as compared to the renal artery has been demonstrated in anoxic dogs.

These facts strongly suggest the kidney as the major site of production of erythropoietin.

There is considerable interest regarding the role of azotemia *per se* in chronic renal failure as a factor disturbing the normal feed-back mechanism. Individuals suffering from renal failure are anemic for at least three reasons: they have chronic hemorrhage; they have red blood cell hemolysis; and they have reduced erythropoiesis. The latter may be due to either or both of actual destruction of erythropoietin-producing tissue and/or toxic inhibition of the bone marrow by as yet unidentified poisons. The latter concept is supported by the fact that after hemodialysis or peritoneal dialysis,

the levels are increased. In addition, infusion of erythropoietin-rich plasma into azotemc nephrectomized animals produces only minimal hematologic improvement. It is suggested that in addition to toxic marrow inhibition, there is also a loss of essential activating cofactors normally supplied by the kidney.

Thus it is apparent that the therapeutic potential for administration of erythropoietin to uremic humans will have to be assessed later, when more is known of the pathological chemistry of this condition.

Finally, it is important to realize that anephric individuals do continue to produce red blood cells albeit at a reduced rate, suggesting extrarenal synthesis. Some authorities claim that about 10% of normal erythropoietin comes from extrarenal sources.

The exact site of intrarenal synthesis is unknown for certainty, although the juxta-glomerular apparatus is strongly suspected.

DYNAMICS OF ERYTHROPOIETIN

After hypoxic stimulation, increased plasma levels occur within 10-30 hours. About 3-5% of the substance is excreted in the urine.

The plasma half-life of injected erythropoietin in hypoplastic anemias is considerably longer than in the anemias associated with erythroid hyperplasia (hemolytic, iron-deficiency etc.), suggesting actual consumption of erythropoietin by erythroid tissue in the latter conditions. Increased activity in hypoplastic anemias is seen only when the hemoglobin is 5 - 7 gm% or lower, but increased levels are detectable in iron-deficiency anemias when the hemoglobin is considerably higher. Increased levels are also seen in thalassemia major, hereditary spherocytosis and sickle cell anemia. These anemias are not due to erythropoietin deficiency, but rather to the marrow's failure to respond to hemolytic demands.

Erythropoietin is probably evoked not only by severe anemic or anoxic stress, but also by normal fluctuations in tissue oxygen within the kidney and extrarenal sites. Tissue oxygenation is influenced by cardiac, pulmonary and endocrine factors, so all of these may increase or decrease the circulating red blood cell count by influencing erythropoietin production.

INCREASED PRODUCTION OF ERYTHROPOIETIN

Increased plasma and urinary activity may be observed in:

(1) most forms of anemia

(2) many patients with arterial desaturation

(3) certain neoplasms (despite normal arterial oxygen saturation)

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These neoplasms may actually secrete erythropoietin.

(4) patients after administration of cobalt salts (causing cellular anoxia)

(5) an active erythropoietic mechanism is found in the fetus, exceeding the maternal production which is in the low normal range. Cord blood has considerable activity and is especially high in anemic or anoxic infants. New born infants with bilateral renal agenesis are not anemic, perhaps reflecting the presence of important extrarenal sites of fetal production.

DECREASED PRODUCTION OF ERYTHROPOIETIN

Decreased plasma and urinary activity may be observed in:

(1) most forms of renal disease (even when patients are anemic). This enigma was discussed above.

(2) some patients with thymomas, in which the plasma shows an inhibitory effect similar to antibody against erythropoietin.

SUMMARY

An outline of the current thinking on the subject of erythropoietin has been presented. The clinician will appreciate that the physiologic basis behind red blood cell regulation is being well established, but with the exception of isolated cases of erythropoietin-secreting tumors and anemias secondary to thymomas, there are no outstanding diseases due to an excess or deficiency of the hormone. Thus, the application of this knowledge to clinical medicine will have to await the development of more sensitive and reliable assay techniques and, if it can prove to be of value, an increased availability to a safe preparation of erythropoietin for therapeutic usage.

D. A. Legge 6T8

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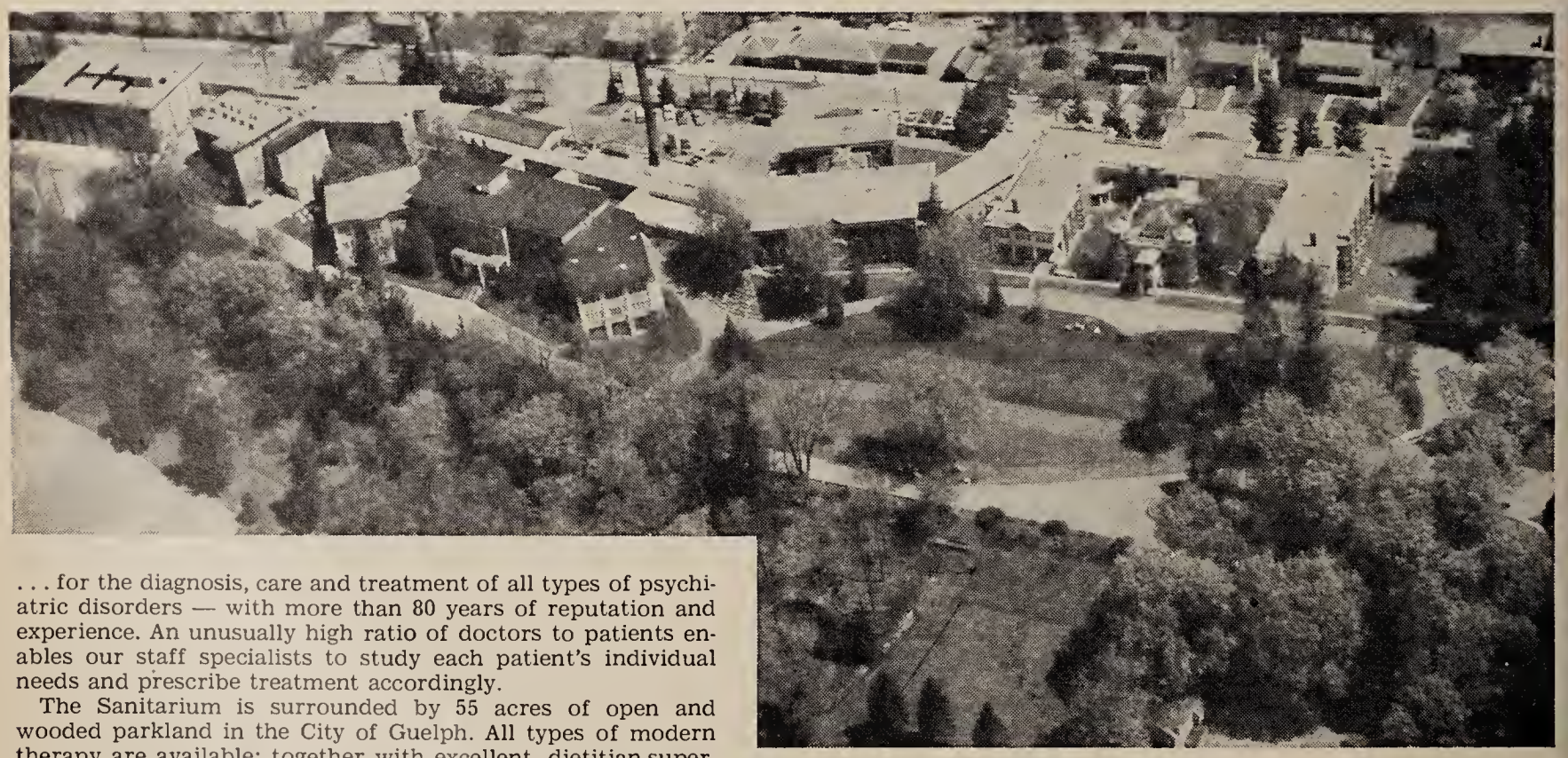

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Clinicopathological Conference

Failure Of Growth And Development And Progressive Renal Impairment In A 15 Year Old Female

CASE PRESENTATION

A 15 year old Italian girl was admitted to hospital because of marked shortness of breath, nausea and vomiting, and generalized weakness.

The history revealed recurrent medical problems dating back to the age of 3½ years. The patient was the full-term product of a normal pregnancy and delivery and was in good health until, at age 3½, she was admitted to hospital with painful, swollen knee joints. It was felt at that time that she had juvenile rheumatoid arthritis (Still's Disease) and this was further verified when she was readmitted at age 4½ and again at 5 with additional involvement of her wrists and temperomandibular joints.

While in hospital at the age of 5 years she was noted to have marked hepatosplenomegaly. This was felt to be due to amyloidosis secondary to Still's Disease but the Congo Red Test was borderline. There were urinary findings also on this admission: urinalysis revealed many granular casts, occasional WBC's, 1 + albumin; BUN was 33 mgm %; urine cultures grew E. coli; the IVP showed loss of function and distortion of the upper urinary tract but normal ureters. The diagnosis of chronic pyelonephritis was made, possibly on the basis of amyloidosis, and she received a course of acromycin therapy while in hospital. In addition, a microcytic, hypochromic anemia with low serum iron was discovered (Hb 7 gm %). This was however, unresponsive to oral iron and transfusions were necessary. A bone marrow study and GI series were not done and she was discharged on oral iron as well as steroids, but apparently no antibiotics.

Her health remained good until the age of 9 except that it was noted that she was small for her age. At age 9 she suddenly devevloped bilateral iritis with the subsequent formation of cataracts, which rendered her almost totally blind.

Over the next 4 years it was noted that the child failed to develop both somatically and with respect to secondary sexual characteristics. But for this, she appeared perfectly normal, her mentality was normal and she was doing quite well at the School for the Blind. Her father, mother and three siblings enjoyed good health and there was no history of renal disease, rheumatoid arthritis, or growth disturbances in any of the members of her family.

Because of her physical retardation she was admitted to hospital at the age of 13, in 1963, for endocrine investigation. This investigation revealed an FSH level less than 5 mouse units /24 hour urine collection, lack of response of the urine steroids to metapirone, and a "staircase" response of the urine steroids to ACTH stimulation. Thyroid function was normal. X-Ray examination revealed no specific abnormalities (including evidence of rheumatoid disease), but her radiological age was estimated at 9 years. Renal status at this time was largely unchanged showing many casts and consistent albuminuria of 3^+; the BUN had risen to 58 mgm %. Serum electrolytes, serum proteins and liver function tests were normal. The hemoglobin was 8 gms % and again transfusions were necessary.

Her next admission occurred in January 1965, when she presented at the emergency department with extreme dyspnoea and fever. Chest examination revealed rales and crepitations throughout the right chest. X-Ray showed patchy, pneumonic infiltrates throughout the right lung field compatible with bronchopneumonia. The heart was normal but the blood pressure was found to be 190/110. She was placed on tetracycline therapy and discharged one week later after the follow-up chest X-Ray became normal.

Ten days later, however, the patient returned again following the sudden onset of dyspnoea. On this admission the only changes of consequence on physical examination were that the blood pressure had risen to 210/110, there was evidence of increased jugular venous pressure, and moist rales were heard in both lung bases. With these signs of early cardiac failure she was placed on digitalis and continued tetracycline therapy. She slowly improved and her respiratory distress subsided considerably. It was now felt that her long standing renal disease had progressed to the end stage with the addition of hypertension, congestive heart failure and uremic pneumonitis. Despite her clinical improvement the BUN remained at 100 mgm % and she was discharged home.

The last admission occurred in late May of the same year with chief complaints of shortness of breath, nausea and vomiting and generalized weakness. Physical examination revealed a tiny, sallow-complexioned girl, who appeared to be about 7 years of age. She had no secondary sexual characteristics (there was no axillary or public hair and no evidence of breast development).

Her height was 49 inches and her weight 48 pounds. She had cervical and axillary lymphadenopathy and marked hepatosplenomegaly. Both knee joints showed evidence of intra-articular effusions. Blood pressure was 210/118, the heart was clinically enlarged but the heart sounds were normal. No murmurs were heard. Basal rales were heard in both lung bases. CNS examination revealed a blind, fully conscious, well oriented child and there were no remarkable sensory or motor findings except for marked neuromuscular irritability. The laboratory findings at this time were as follows: urinalysis: many granular casts, 3-4^{+} albuminuria, occasional RBC's and WBC's; hematology: Hb 7 grams %, hypochromic, microcytic blood smear, ESR 95; blood chemistry: calcium 5.8 mgm %, potassium 3.9 mEq./L; sodium 137.5 mEq./L, chlorides 83 mEq./L, uric acid 6.5 mgm %, BUN 180 mgm %.

Over the course of the next three weeks the BUN slowly rose to a high of 252 mgm %, the patient had increasing gastro-intestinal symptoms, and despite supportive therapy she became confused, comatose and expired on June 5th, 1965.

In summary, a 15 year old Italian female presented with typical signs and symptoms of renal failure, ultimately progressing to death. Past history included uremia, pyelonephritis, anemia, juvenile rheumatoid arthritis, iritis and hyopituitarism.

DIFFERENTIAL DIAGNOSIS

In the evaluation of patients such as this, endocrine disorders are of prime consideration in the differential diagnosis, especially since hypopituitarism is among the commonest causes of stunted growth. Because of the findings of massive albuminuria, hypertension, a long history of chronic pyelonephritis, GI disturbances, arthritis etc. systemic or metabolic disorders cannot be excluded as a cause of developmental retardation.

Endocrine Disorders

This patient exhibited pituitary insufficiency as evidenced by stunted growth and failure of development of secondary sexual characteristics. The laboratory examination supports this contention as shown by a low FSH assay of less than 5 mouse units, 24 hour urinary excretion of 17 OH-steroids that did not respond to metapirone, and an abnormal response to the ACTH test. A human growth hormone (HGH) assay would have been helpful, especially if low levels of the hormone were found. Thyroid function tests were normal.

Because of more refined techniques in anterior pituitary hormone assays, several authors have described isolated deficiencies of the different hormones in cases of hypopituitarism from various causes. This probably explains the normal thyroid function tests in this patient.

It has been postulated that the order of frequency of hormonal loss in hypopituitarism is as follows; HGH, FSH (gonadotrophin) ACTH, TSH. Diversity in appearance of patients with pituitary insufficiency is probably explained on this basis.

This is therefore most likely a cause of prepuberal hypopituitarism producing a pituitary dwarf. The cause

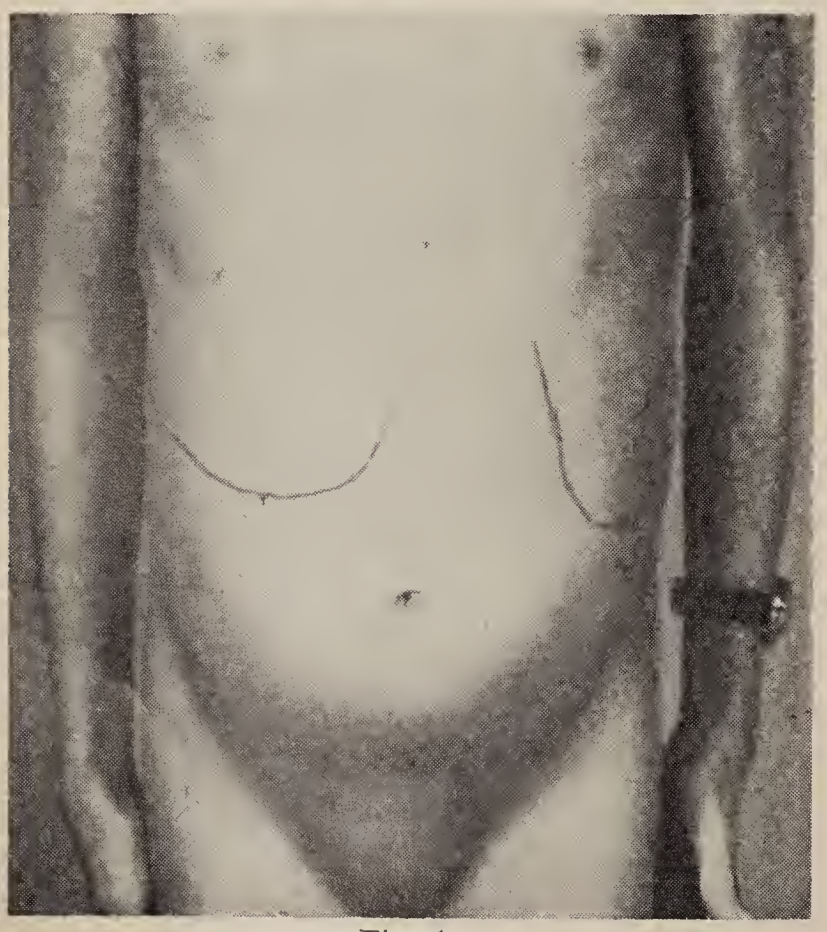

Fig. 1.
Demonstrating hepatosplenomegaly, and failure of development in 15 year old child.

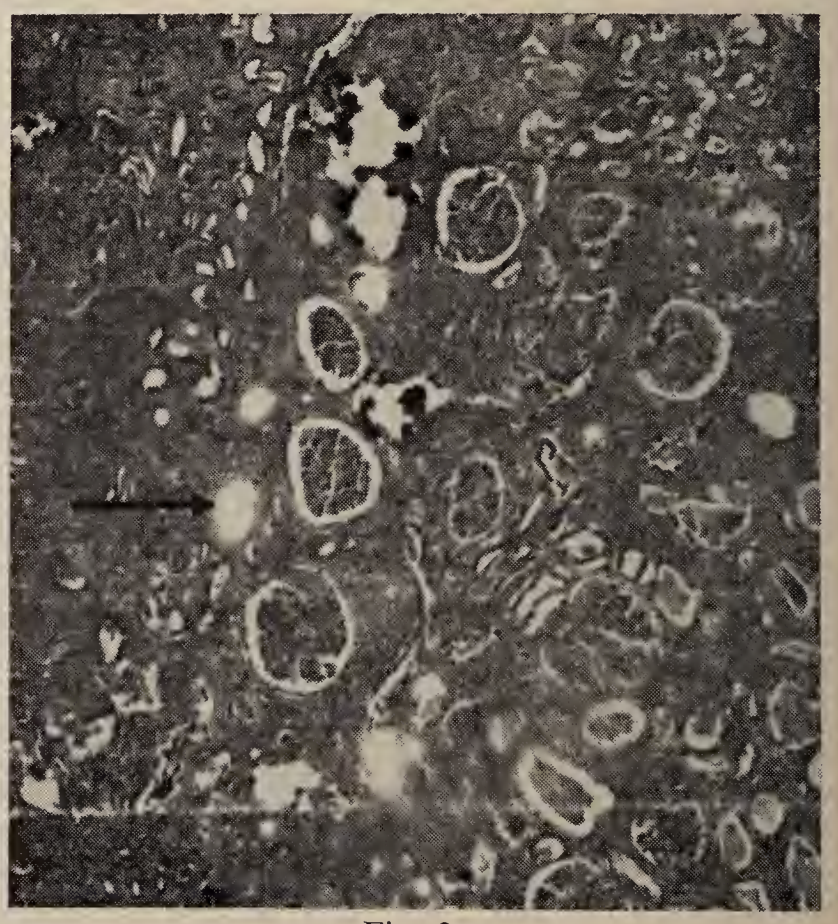

Fig. 2.
Crystal deposition, extensive fibrosis, and areas of calcification in kidney.

of the disorder is usually associated with a suprasellar cyst or a craniopharyngioma. In retrospect, she could have had more tests of value in making a diagnosis such as a pneumoencephalogram, a tomogram or carotid arteriograms.

In a genetic dwarf, the endocrine function studies are usually within normal limits.

Systemic and Metabolic Disorders

Systemic and metabolic disorders as a cause of stunted growth cannot be excluded in this patient because of signs and symptoms indicating involvement of several organ systems as manifested by the shortness of breath, gastrointestinal disturbances (nausea and vomiting) neuromuscular irritability, arthritis, hypertension, marked albuminuria, azotemia, hypochloremia and hypocalcemia. Of the systemic metabolic disorders causing developmental disturbances, that is renal, cardiac, pulmonary, intestinal, storage diseases etc., renal disorders are by far the most common.

Renal dwarfism may be caused by malformation or obstruction of the urinary tract or by an inherited disorder of tubular function, that is, renal tubular acidosis.

Lightwood's Syndrome (renal tubular acidosis syndrome) generally begins in infancy and is associated with excessive calcium excretion. The primary difficulty is the inability to produce urine of normal acidity. Acidic metabolites are excreted with fixed base so that losses of sodium, potassium and calcium occur. The acidosis is characterised by low plasma bicarbonate, decreased plasma inorganic phosphorus but, in contrast to our case, hyperchloremia as well.

Renal dwarfism is seen also in cases of obstruction at the outlet of the bladder which produces back pressure and hydronephrosis; or it may be due to congenital cystic disease, congenital hypoplasia of the kidneys or most commonly chronic pyelonephritis.

In the case of chronic pyelonephritis the distal tubules loose the ability to preserve acid-base balance with the result that there is a lowering of serum calcium levels, which appears to cause a secondary hyperparathyroidism. The increased parathyroid hormone will cause increased osteoclastic activity and enhance bone resorption. Likewise a secondary hyperparathyroidism will cause diminished tubular reabsorption of phosphate. The resulting bone disease is that of classical rickets (renal rickets) or osteomalacia. However X-ray studies in our patient showed no abnormalities such as bowing of the bones, uncalcified osteoid seams, or "moth-eaten" epiphyses which would be seen if this was the only process at work leading to the developmental retardation.

With the protean manifestations exhibited in this case, diseases such as amyloidosis, which with its diverse clinical forms may mimic a number of other clinical entities, cannot be excluded from the differential diagnosis. Secondary amyloidosis, which is found in 25% of patients with rheumatoid arthritis, is manifested by the nephrotic syndrome with renal involvement but rarely if ever by signs of insufficiency of function when endocrine glands are infiltrated.

As a cause of dwarfism the genetic mucopolysaccharidoses can be excluded for the patient although retarded in growth showed none of the cardinal features which include unusual facies, lumbar gibbus, radiologic changes from involvement of the osseous skeleton and mental retardation.

A single diagnosis which would encompass all signs and symptoms in this case cannot be made from the above data. In all probability there must be at least two conditions operating here; a prepuberal pituitary dwarfism, and chronic renal disease producing azotemia and uremia.

POST MORTEM FINDINGS

The subject was a 15 year old white female child who appeared to be 6 years of age. She was grossly retarded in growth, weight, length and development. There was generalized atrophy of muscles. The skin was dry, pale and somewhat ashen grey in colour. The breasts were undeveloped as were the external genitalia. There was no pubic or axillary hair.

Gross findings were as follows: The pericardial cavity contained 50 cc's of amber coloured clear fluid. The pericardium was marked by shaggy greyish-white fibrinous material. The heart weighed 245 grams. The left ventricle was hypertrophied and measured 1.5 cm's in thickness.

Each pleural cavity contained about 100 cc's of amber coloured fluid. The pleural surfaces were marked by patchy, greyish-white, firm consolidated areas and on sectioning both lungs, diffuse bronchopneumonia was discovered.

There was generalized lymphoid hyperplasia involving cervical, mediastinal, hilar, mesenteric, peri-aortic and pelvic lymph nodes.

The liver was enlarged to about 4 fingers below the right costal margin. It weighed 1210 grams and cut surfaces were greyish-red and appeared congested.

Both adrenals were small, the combined weight was 5.5 grams.

The right kidney weighed 32 grams and the left only 18 grams. They were contracted and their capsules stripped easily, revealing rough granular surfaces. There were depressed areas of scar tissue. On sectioning of both kidneys, the substance felt firm and gritty. The pyramids of both were greyish-white in colour and showed tiny areas of sand-like material. The outline between cortex and medulla was completely lost.

The uterus was hypoplastic and both adnexae were small and underdeveloped.

Microscopic examination revealed the following pertinent findings:

The sections of the heart showed chronic pericarditis with perivascular infiltration of chronic inflammatory cells and some fibrous deposition. Sections of the coronary artery within the pericardium showed marked proliferative intimal thickening, giving the appearance of atherosclerosis.

Sections of lung showed a rather diffuse interstitial pneumonitis of chronic nature with interstitial fibrosis. Many alveoli particularly in the lower lobes were filled with inflammatory cells and showed patchy bronchopneumonia.

Sections of lymph nodes from all parts of the body revealed a granulomatous response with a great deal of productive fibrosis and numerous giant cells. These giant cells were clustered around crystal-like material, and this same material was seen in many of the giant cells.

The crystals were refractile to polarized light and were faintly greenish-yellow, tending to be rhomboidal or "sheaf-of-wheat" in pattern.

These same crystals were found throughout the bone marrow, but here there did not seem to be a significant giant cell response.

In the kidney sections there was found severe, diffuse pyelonephritis with a thickened Bowman's capsule and hyalinization of the glomeruli. Throughout the kidneys could be seen granular calcific desposits and deposits of the crystals previously described.

The sections of the pituitary gland showed some foci of calcification and crystal deposition but the gland was not totally destroyed by the process.

In summary, the pathological evidence demonstrated the findings of end stage renal disease. The interesting feature of this case however, was the presence of oxalate crystals which were particularly demonstrable in the kidney, lymph nodes, bone marrow and pituitary gland. It would appear that this child demonstrated primary hyperoxaluria, a condition which appears to result from an abnormal glyoxylate metabolism producing a progressive bilateral calcium oxalate urolithiasis and nephrocalcinosis which begins early in childhood and usually terminates fatally in childhood or early adulthood.

DISCUSSION

Oxalosis is a condition characterized by deposition of calcium oxalate in many tissues of the body: its most important manifestations are due to calcium oxalate urolithiasis and nephrocalcinosis which, combined with recurrent urinary tract infection, lead to destruction of kidney tissue and death in childhood or early adulthood from renal failure and hypertension. The only constant biochemical abnormality is a continuously high (350 mg/day) urinary excretion of oxalates. It should be considered in all cases of children with stones in the urinary tract. It is rare, the 25th case being reported by Shepard et al in 1960. Its mode of inheritance has not been worked out. Archer considered it to be an autosomal recessive: Shepard et al thought it was an autosomal dominant on the basis of their studies. They reviewed Archer's material and agreed that his cases appeared recessive. The only difference between the two was the presence of an increased blood uric acid in the type with dominant inheritance, and on this basis Shepard questioned the possibility of a second form of the disease accompanied by an increase in uric acid in the blood.

Once formed, oxalate appears to be metabolically inert. No evidence of a pathway of destruction of oxalate in mammals has been obtained. Labelled oxalate when given is recovered 89-99% unchanged in the urine. Its mechanism of excretion in the kidney is not clear either.

Regarding the source of the high urinary oxalates there is general agreement that it is not due either to an increased ingestion of oxalates in the diet or to increased absorption in the G.I. tract. The patients excrete increased oxalate whether the oxalate ingestion is increased, decreased, or abolished altogether (as when a patient is on I.V. glucose for several days). The mechanism of its endogenous derivation is far from clear. Glyoxylic acid is the only known direct precursor of oxalic acid in mammals. Most of the glyoxylic acid is thought to be derived from glycine. If labelled glycine is given, urinary oxalates become highly labelled within a few hours. Oxalate synthesis from glycine becomes appreciable only when the glyoxylic acid pool in the body is greatly expanded, suggesting that in oxalosis a block in glyoxylic acid metabolism may exist. As noted in the following diagram glyoxylate may have other precursors than glycine.

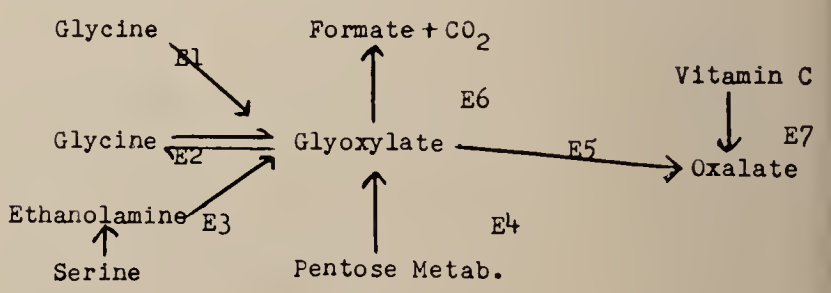

Fig. 3.

The main changes are in the kidneys where the pelves and calyces contain yellow or tan coloured stones composed mainly of calcium oxalate. The cortical surfaces of the kidneys are granular and stippled with small yellow flecks. They impart a gritty sensation when

cut and on microscopic examination this is seen to be due to extensive deposition of calcium oxalate crystals. These are faintly greenish-yellow, tend to be rhomboidal and arranged in "rosette" or "sheaf-of-wheat" pattern. They are seen in the glomeruli, lumina of tubules, and interstitial tissue. Secondary inflammatory changes in the kidney are the rule. The generalized distribution may be best described by listing the reported sites of crystal deposition: myocaridum, lungs, tracheal cartilage, muscle layers of G.I. tract, bone, bone-marrow, cartilage, lymph nodes, spleen, thymus, liver, thyroid, adrenals, pituitary, pancreas, parathyroid, testis, and even in the walls of arteries. The crystals do not seem to excite any significant foreign body reaction. Apart from the crystals, most of the organs are unremarkable except for the kidneys. Some changes may be seen secondary to the kidney disease such as parathyroid hyperplasia and renal rickets—some of these patients have even undergone parathyroid exploration.

S. J. Cartan 6T9

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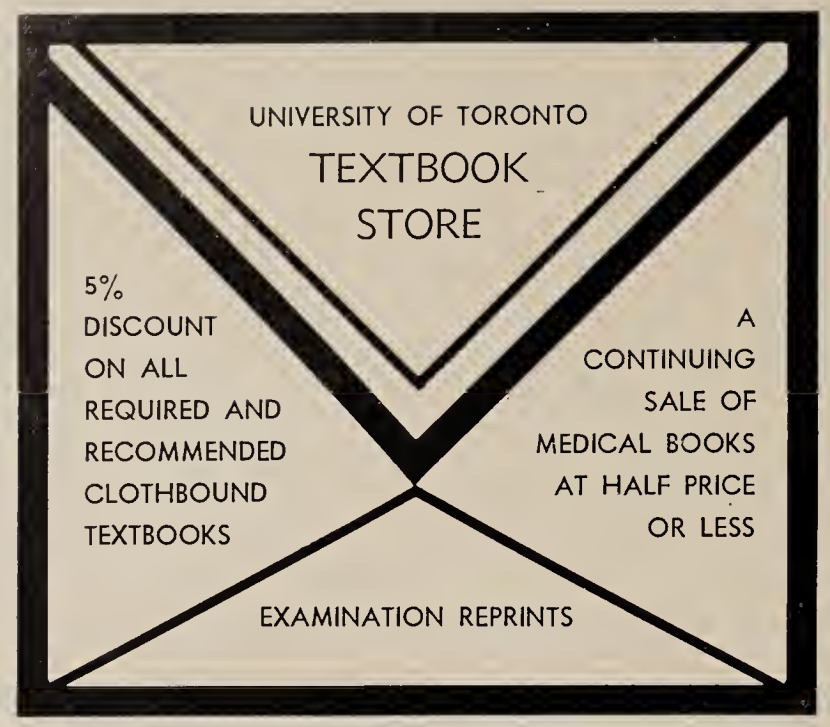

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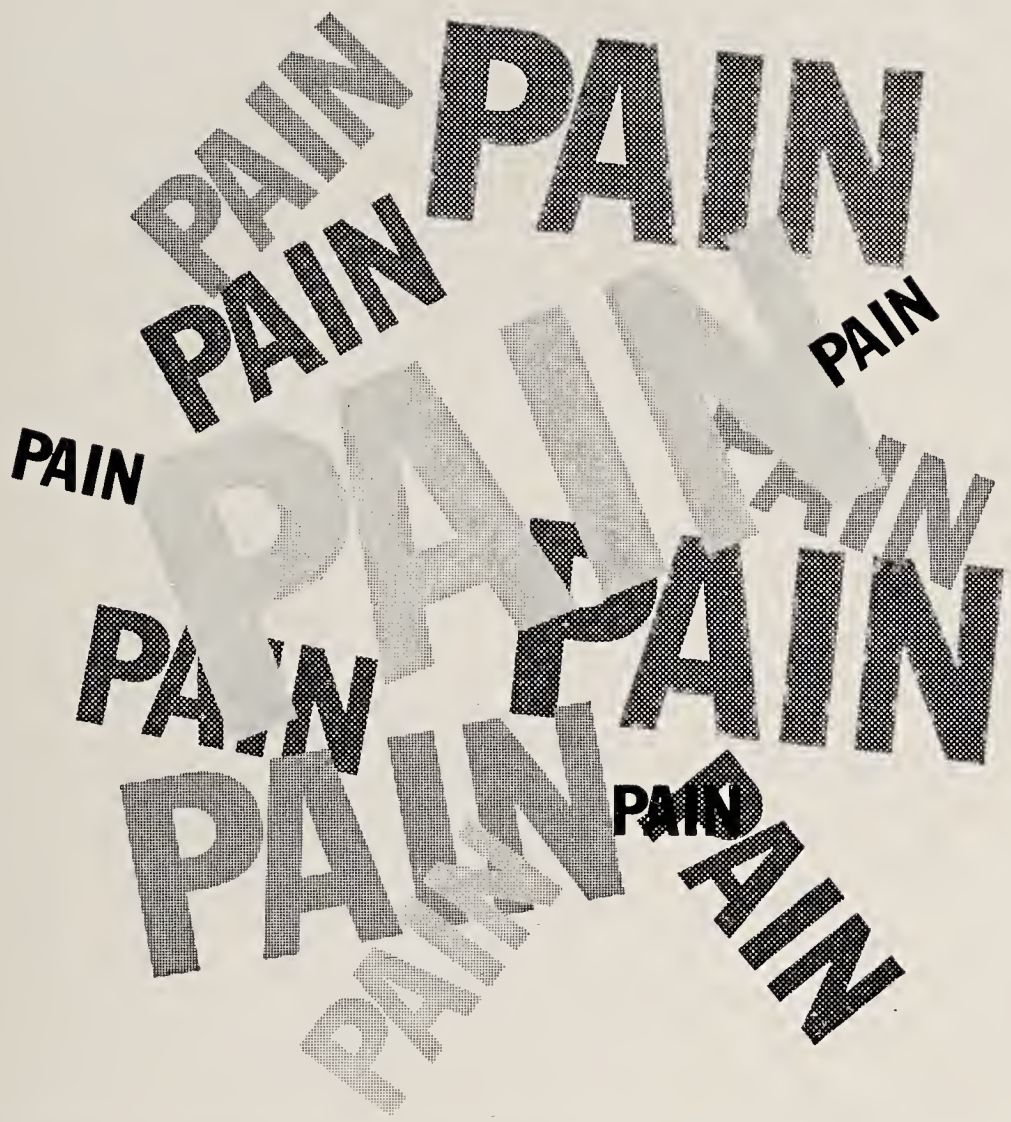

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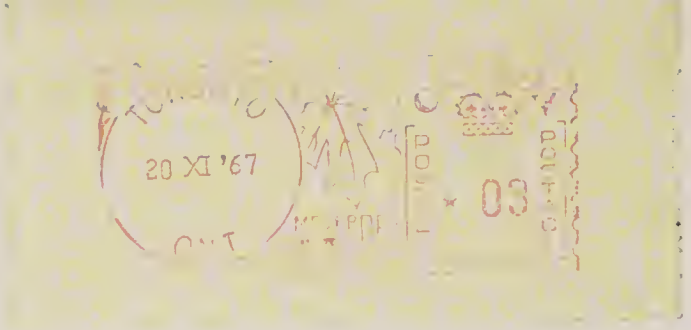

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